Journal of
THE CHEMICAL SOCIETY

Publication Committee

Chairman : C. K. Ingold, D.Sc., F.R.I.C., F.R.S.

G. Baddeley, Ph.D., D.Sc., F.R.I.C.
D. H. R. Barton, D.Sc., F.R.I.C., F.R.S.
C. E. H. Bawn, B.Sc., Ph.D., F.R.S.
D. J. Bell, Sc.D., Ph.D.
E. J. Bowen, M.A., D.Sc., F.R.S.
H. Burton, Ph.D., D.Sc., F.R.I.C.
J. Chatt, M.A., Ph.D., F.R.I.C.
C. A. Coulson, M.A., D.Sc., F.R.S.
H. J. Emeléus, D.Sc., A.R.C.S., F.R.S.
F. Fairbrother, D.Sc.
R. D. Haworth, D.Sc., Ph.D., F.R.S.
B. A. Hems, D.Sc., F.R.I.C.
E. D. Hughes, D.Sc., F.R.I.C., F.R.S.
H. R. Ing, M.A., D.Phil., F.R.S.
H. M. N. H. Irving, M.A., D.Phil., F.R.I.C.
E. R. H. Jones, D.Sc., F.R.I.C., F.R.S.
F. G. Mann, Sc.D., F.R.I.C., F.R.S.
R. A. Morton, D.Sc., Ph.D., F.R.S.
R. G. W. Norrish, Sc.D., F.R.I.C., F.R.S.
L. N. Owen, Ph.D., D.Sc., F.R.I.C.
M. W. Perrin, C.B.E., M.A., F.R.I.C.
H. M. Powell, M.A., B.Sc., F.R.S.
N. Sheppard, M.A., Ph.D.
C. W. Shoppee, D.Sc., D.Phil., F.R.I.C.
W. F. Short, D.Sc., M.Sc.
R. Spence, C.B., Ph.D., D.Sc., F.R.I.C.
M. Stacey, Ph.D., D.Sc., F.R.S.
L. E. Sutton, M.A., D.Phil., F.R.S.
H. W. Thompson, M.A., D.Sc., F.R.S.
E. E. Turner, M.A., D.Sc., F.R.S.
J. Walker, Ph.D., D.Phil., D.Sc.
W. Wardlaw, C.B.E., D.Sc., F.R.I.C.
W. A. Waters, Sc.D., F.R.I.C., F.R.S.

Editor

R. S. Cahn, M.A., D.Phil.Nat., F.R.I.C.

Assistant Editors

A. D. Mitchell, D.Sc., F.R.I.C.
L. C. Cross, Ph.D., A.R.C.S., F.R.I.C.
A. E. Somerfield, B.A., B.Sc.

OCTOBER, 1954

Subscription rate to non-Fellows £10 0s. 0d. per annum post free

LONDON: THE CHEMICAL SOCIETY, BURLINGTON HOUSE, W.1.

THE CHEMICAL SOCIETY

PATRON
HER MAJESTY THE QUEEN

President
W. Wardlaw, C.B.E., D.Sc., F.R.I.C.

Vice-Presidents
who have filled the office of President

Sir Ian Heilbron, D.S.O., D.Sc., LL.D., F.R.S.
Sir Cyril Hinshelwood, M.A., Sc.D., F.R.S.
C. K. Ingold, D.Sc., F.R.I.C., F.R.S.
W. H. Mills, M.A., Sc.D., F.R.S.
Sir Eric Rideal, M.B.E., M.A., D.Sc., F.R.S.
Sir Robert Robinson, O.M., D.Sc., LL.D., F.R.S.

Vice-Presidents

R. D. Haworth, D.Sc., Ph.D., F.R.S.
E. L. Hirst, D.Sc., LL.D., F.R.S.
E. R. H. Jones, D.Sc., F.R.I.C., F.R.S.
R. P. Linstead, C.B.E., M.A., D.Sc., F.R.S.
H. W. Melville, D.Sc., F.R.I.C., F.R.S.
Sir John Simonsen, D.Sc., F.R.I.C., F.R.S.

Honorary Treasurer
M. W. Perrin, C.B.E., M.A., F.R.I.C.

Honorary Secretaries

H. Burton, Ph.D., D.Sc., F.R.I.C.
E. D. Hughes, D.Sc., F.R.I.C., F.R.S.
L. E. Sutton, M.A., D.Phil., F.R.S.

Ordinary Members of Council

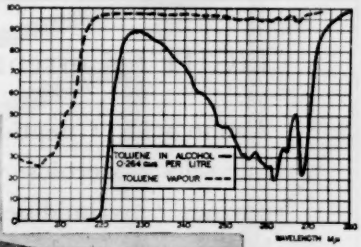
C. C. Addison, D.Sc., Ph.D., F.R.I.C.
V. C. Barry, D.Sc., M.R.I.A., F.I.C.I., F.R.I.C.
D. H. R. Barton, D.Sc., F.R.I.C., F.R.S.
F. Bergel, D.Phil.Nat., D.Sc., F.R.I.C.
E. J. Bourne, Ph.D., D.Sc., A.R.I.C.
E. A. Braude, Ph.D., D.Sc., F.R.I.C.
Neil Campbell, D.Sc., Ph.D.
J. Chatt, M.A., Ph.D., F.R.I.C.
M. J. S. Dewar, M.A., D.Phil.
I. J. Faulkner, B.Sc., Ph.D., F.R.I.C.
S. J. Gregg, Ph.D., A.R.C.S., F.R.I.C.
H. M. N. H. Irving, M.A., D.Phil., F.R.I.C.
Brynmor Jones, Sc.D., Ph.D., F.R.I.C.
F. B. Kipping, M.A., Ph.D.
E. A. Moelwyn-Hughes, D.Phil., D.Sc., Sc.D.
A. Robertson, M.A., Ph.D., F.R.S.
J. M. Robertson, M.A., D.Sc., F.R.S.
M. A. T. Rogers, B.Sc., Ph.D., A.R.I.C.
H. N. Rydon, D.Sc., D.Phil., F.R.I.C.
H. D. Springall, M.A., D.Phil., F.R.I.C.
A. I. Vogel, D.Sc., D.I.C., F.R.I.C.

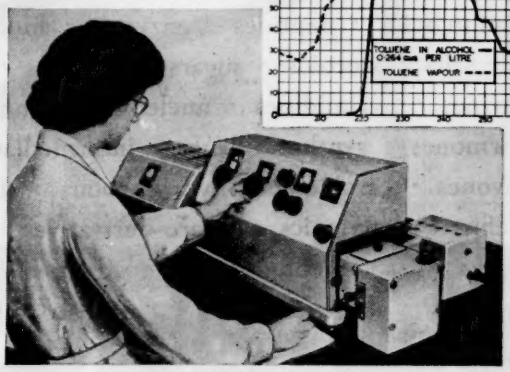
General Secretary
J. R. Ruck Keene, M.B.E., T.D., B.A.

Librarian
A. E. Cummins

Telephone Numbers : Regent 0675/6

UNICAM
SPECTROPHOTOMETERS

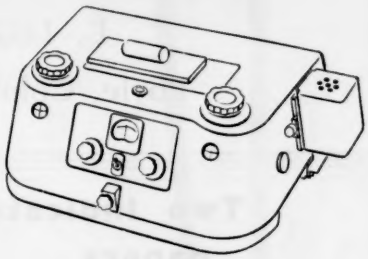




SP.500

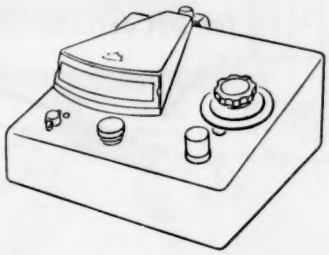
The well-known Unicam Quartz Spectrophotometer makes possible analysis by light absorption measurement at all wavelengths from 2,000Å to 10,000Å. The quality of its performance and simplicity of operation combine to make the instrument ideally suitable for research, process control or routine determinations.

SP.600



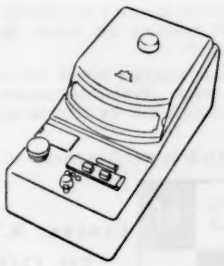
This new spectrophotometer offers at moderate price the many advantages of up-to-date analytical methods. The high resolution of the glass prism monochromator combined with a reliable electronic system gives exceptional performance in the visible range (3,600—10,000Å).

SP.400



Chemists in clinical or biochemical laboratories appreciate the diffraction grating fitted in this absorptiometer which allows them to follow an end point in a changing system. A use will be found for this reliable instrument in almost every laboratory.

SP.300



The demand for a simple, robust filter-type colorimeter giving a consistently high performance over long periods is amply met by the Unicam SP.300 Colorimeter. New applications are continually being found for this reliable, inexpensive instrument that is strongly built and easy to operate.

Illustrated leaflets describing any of these instruments in detail will gladly be sent on request.

UNICAM INSTRUMENTS LTD · ARBURY WORKS · CAMBRIDGE
U125 JNRTX

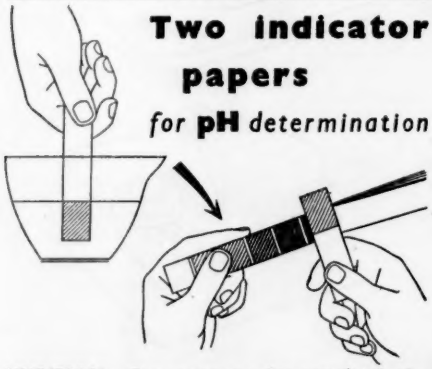
LIGHT'S Current catalogue lists:—

Amino acids · peptides · enzymes · biochemicals
bile salts · steroids · sugars · vitamins · alkaloids
purines · pyrimidines · nucleotides · nucleosides
hormones · synthetic drugs · intermediates · reagents
flavones · carcinogenic hydrocarbons · silanes
olefins · acetylenics · fluoro-derivatives · nitriles
fatty acids and alcohols · filter aids · solvents · metal
hydrides · ion exchangers · chromatographic aids.

Please write for your copy to :—

L. LIGHT & Co. Ltd.
Poyle, Colnbrook, Slough, Bucks.

Two indicator papers
for **pH** *determination*



UNIVERSAL One paper covering completely the range from 1 to 10 enabling pH values to be checked to within 0.5 pH.

COMPARATOR Four separate books for work requiring greater accuracy. With these papers the pH value of any solution can be ascertained to within 0.3 pH.

Descriptive leaflet will be sent free on request.

JOHNSONS OF HENDON LTD
London, N.W.4
Est. 1743

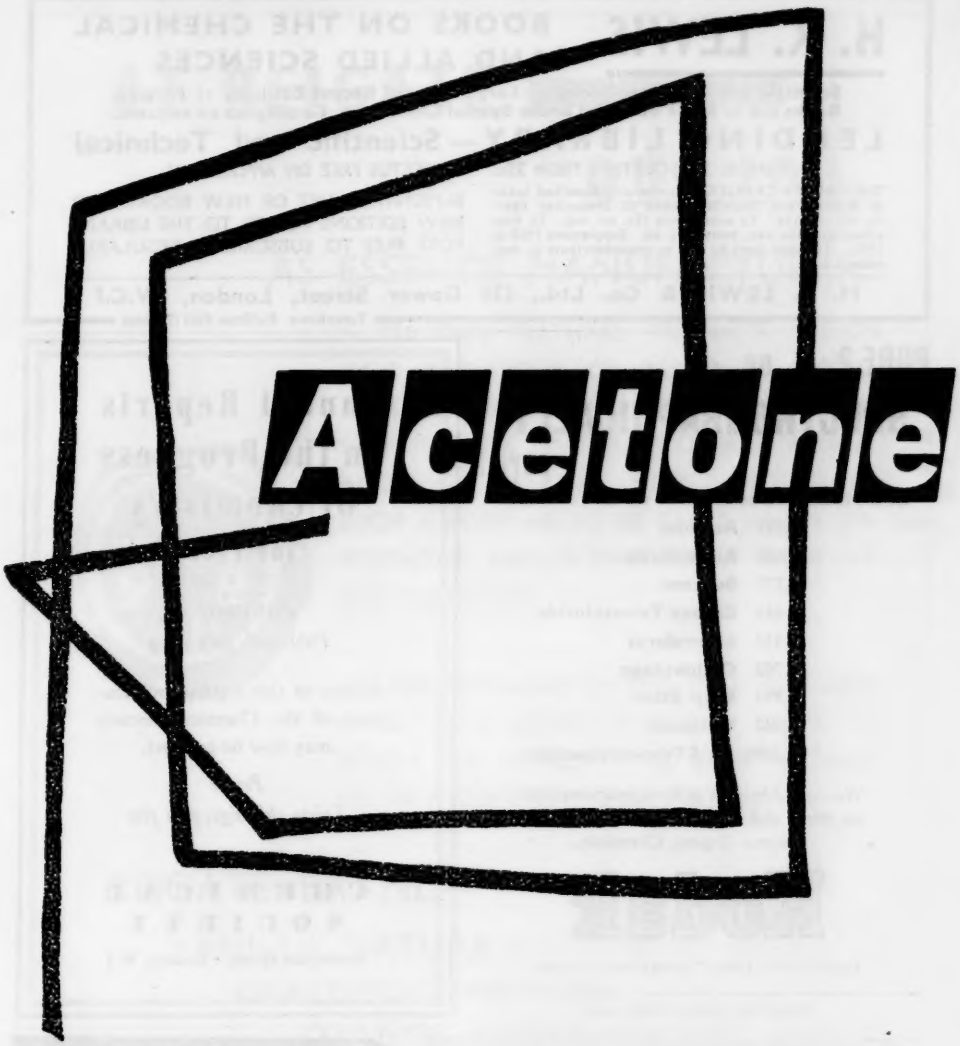
We are makers of :

ALUMINIUM NITRATE
TIN SULPHATE
(STANNOUS)

Samples and quotations from:

KAYLENE BRAND

KAYLENE (CHEMICALS) LTD.
WATERLOO ROAD, LONDON, N.W.2



SHELL **Shell Chemicals Limited**
(DISTRIBUTORS)

Norman House, 105-109 Strand, London, W.C.2. *Telephone : Temple Bar 4455*

Divisional Offices:

LONDON : Walter House, Bedford Street, W.C.2. *Tel : Temple Bar 4455.*
MANCHESTER : 42 Deansgate. *Tel : Deansgate 6451.*
BIRMINGHAM : Clarence Chambers, 39 Corporation Street, 2. *Tel : Midland 6954.*
GLASGOW : 28 St. Enoch Square, C.1. *Tel : Glasgow Central 9861*
BELFAST : 35-37 Boyne Square. *Tel : Belfast 20281.*
DUBLIN : 53 Middle Abbey Street. *Tel : Dublin 45775.*

H. K. LEWIS **BOOKS ON THE CHEMICAL AND ALLIED SCIENCES**

Scientific and Technical Books. :: Large Stock of Recent Editions. :: Foreign Books not in Stock obtained under Special Licence. :: Catalogues on request.

LENDING LIBRARY—Scientific and Technical

ANNUAL SUBSCRIPTION FROM **25s.** *PROSPECTUS FREE ON APPLICATION*

THE LIBRARY CATALOGUE containing classified Index of Authors and Subjects revised to December 1949. Pp. xii + 1152. To subscribers 17s. 6d. net. To non-subscribers 35s. net., postage 1s. 6d. Supplement 1950 to 1952. To subscribers 3s. net; to non-subscribers 6s. net; postage 6d.

BI-MONTHLY LIST OF NEW BOOKS AND NEW EDITIONS ADDED TO THE LIBRARY POST FREE TO SUBSCRIBERS REGULARLY

H. K. LEWIS & Co. Ltd., 136 Gower Street, London, W.C.1

Telephone: EUSton 4282 (7 lines)

PURE ? . . . or

SPECTROGRAPHICALLY pure ?

Of the latter kind of chemicals we have in stock:—

S.297 **Acetone**
S.488 **Acetonitrile**
S.777 **Benzene**
S.444 **Carbon Tetrachloride**
S.337 **Chloroform**
S.702 **Cyclohexane**
S.997 **Ethyl Ether**
S.467 **Methanol**
S.2396 **2:2:4-Trimethylpentane**

We should be glad to have your enquiries for these and for any of the other 3,500 Eastman Organic Chemicals.

Kodak

Kodak Limited, Kirkby Trading Estate, Liverpool

'Kodak' is a registered trade-mark

Annual Reports on the Progress of Chemistry for 1953

VOLUME L

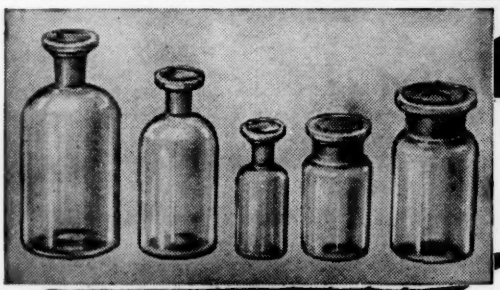
Published July 1954

Copies of this regular publication of the Chemical Society may now be ordered.

Price:
Thirty shillings, post free

THE CHEMICAL SOCIETY

Burlington House · London, W.1



BEATSON CLARK BOTTLES

Dustproof stoppered reagents

When ordering your Laboratory requirements be sure to specify Beatson Clark Dustproof Stoppered Reagent Bottles.

"The Sign of a *Good Bottle"*

BEATSON, CLARK & CO. LTD.
GLASS BOTTLE MANUFACTURERS
ROTHERHAM *Established 1751* **YORKS**

BC 75

AT REIGATE

OUR JOB

AS ESSENCE MANUFACTURERS

IS TO TAKE NATURAL PRODUCTS WHICH HAVE A FLAVOUR OR AROMA OR BOTH; EXTRACT FROM THEM THE PRINCIPLES RESPONSIBLE FOR THAT FLAVOUR AND AROMA, AND THEN PREPARE THESE PRINCIPLES IN SUCH A FORM AS TO BE EASILY AND CONVENIENTLY AND ECONOMICALLY USED BY OUR CUSTOMERS.

WE ARE SPECIALISTS IN THIS FIELD AND CAN OFFER GUARANTEED NATURAL PRODUCTS WHICH FOR QUALITY AND TRUE FLAVOUR ARE IN A CLASS BY THEMSELVES.

REIGATE BRAND—

VANILLA NATURA
GRAPEFRUIT NATURA
ORANGE NATURA
(SWEET OR BITTER)
ORRIS NATURA

WHITE, TOMKINS & COURAGE, LTD.
NORTH ALBERT WORKS, REIGATE

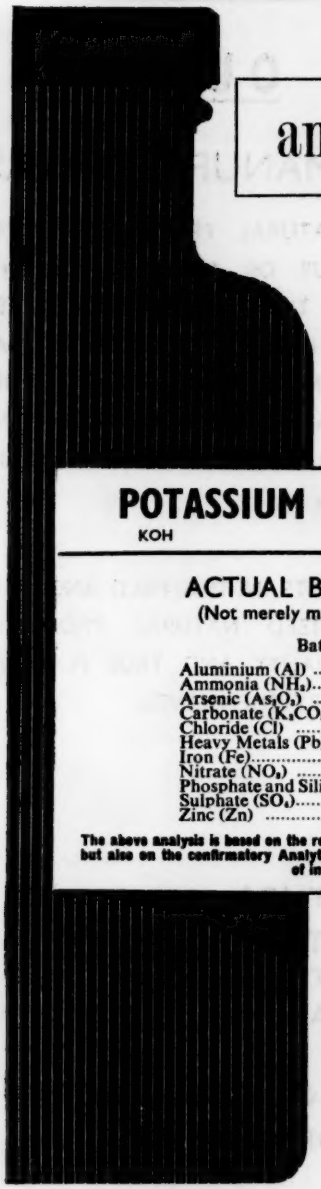
TELEGRAMS: ESSWHITE, REIGATE **TELEPHONE: REIGATE 2242–3**

ESTABLISHED 1841

Judactan

analytical reagents

with actual batch analysis



POTASSIUM HYDROXIDE A.R.

KOH Mol. Wt. 56·10

ACTUAL BATCH ANALYSIS

(Not merely maximum impurity values)

Batch No. 70501

Aluminium (Al)	0·0003%
Ammonia (NH_3)	0·0002%
Arsenic (As_2O_3)	no reaction
Carbonate (K_2CO_3)	0·6%
Chloride (Cl)	0·0007%
Heavy Metals (Pb)	0·0004%
Iron (Fe)	0·0004%
Nitrate (NO_3)	no reaction
Phosphate and Silicate (PO_4)	0·0005%
Sulphate (SO_4)	0·0005%
Zinc (Zn)	0·0005%

The above analysis is based on the results, not of our own Control Laboratories alone, but also on the confirmatory Analytical Certificate issued by independent Consultants of international repute

Chemists all over the world are grateful for our care. Our policy of having independent analyses made gives chemists added confidence in their work.

Why not compare the actual batch analysis shown with the purities guaranteed by the specifications to which you normally work? You will find the comparison of interest and almost certainly of help to you.

The General Chemical & Pharmaceutical Co. Ltd., Chemical Manufacturers, Judex Works, Sudbury, Middlesex.

CONTENTS.

PAPERS COMMUNICATED TO THE CHEMICAL SOCIETY.

General, Physical, and Inorganic.

PAGE

The Structure of Overcrowded Aromatic Compounds. Part I. A Preliminary Survey.
By E. HARNIK, F. H. HERBSTEIN, G. M. J. SCHMIDT, and (in part) F. L. HIRSHFELD . 3288

The Structure of Overcrowded Aromatic Compounds. Part II. The Crystal Structure of Dianthronylidene.
By E. HARNIK and G. M. J. SCHMIDT 3295

The Structure of Overcrowded Aromatic Compounds. Part III. The Crystal Structure of 3 : 4-Benzophenanthrene.
By F. H. HERBSTEIN and G. M. J. SCHMIDT 3302

The Structure of Overcrowded Aromatic Compounds. Part IV. The Crystal Structure of Tetrabenzonaphthalene.
By F. H. HERBSTEIN and G. M. J. SCHMIDT 3314

The Oxides of Uranium. Part IV. The System UO_2–ThO_2–O.
By J. S. ANDERSON, D. N. EDGINGTON, L. E. J. ROBERTS, and (in part) E. WAIT . 3324

The Oxides of Uranium. Part V. The Chemisorption of Oxygen on UO_2 and on UO_2–ThO_2 Solid Solutions.
By L. E. J. ROBERTS 3332

The Oxidation of Copper and Zinc.
By E. R. S. WINTER 3342

Magnetochemistry of the Heaviest Elements. Part VIII. Metallic Plutonium.
By J. K. DAWSON 3393

The Analysis of Inorganic Compounds by Paper Chromatography. Part VI. Further Studies on the Separation and Detection of Lanthanons.
By F. H. POLLARD, J. F. W. MCOMIE, and H. M. STEVENS 3435

Solubilities of the Inert Gases in Water.
By T. J. MORRISON and N. B. JOHNSTONE 3441

The Chromatography of Gases and Vapours. Part IV. Applications of the Surface-potential Detector.
By J. H. GRIFFITHS and C. S. G. PHILLIPS 3446

Calculations on the Electronic Spectra of *trans*-Butadiene by a Semi-empirical Molecular-orbital Approximation.
By CARL M. MOSER 3455

Tertiary Alkoxides of Thorium.
By D. C. BRADLEY, M. A. SAAD, and W. WARDLAW 3488

Nitryl Fluoride as a Nitrating Agent.
By G. HETHERINGTON and P. L. ROBINSON 3512

Esters of Inorganic Oxyacids. Part I. The Mechanism of Hydrolysis of Alkyl Esters, ^{18}O being used as Tracer, and its Relation to other Reactions in Alkaline Media.
By M. ANBAR, I. DOSTROVSKY, DAVID SAMUEL, and A. D. YOFFE 3603

NOTES :

The Compound of Antimony Pentachloride with Nitric Oxide.
By H. J. M. BOWEN 3637

The Kinetics of the Oxidation of Propylene by Nitrogen Dioxide.
By T. L. COTTRELL and T. E. GRAHAM 3644

Physical Organic.

Electronic Spectra of Some Aromatic Mercury Compounds.
By G. LEANDRI and A. TUNDO 3377

Kinetics of the Pyrolysis of Trimethylarsine, Tristrifluoromethylarsine, and Related Compounds.
By P. B. AYSCOUGH and H. J. EMELÉUS 3381

PAGE

Alkyl–Oxygen Fission in Carboxylic Esters. Part XIV. 4-Methyldiphenylmethyl and 2 : 4 : 6-Trimethyldiphenylmethyl Compounds.
By A. G. Davies, J. Kenyon, B. J. Lyons, and T. A. Rohan 3474

The Influence of Ring Size upon the Stability of Metal Chelates.
By H. Irving, R. J. P. Williams, D. J. Ferrett, and A. E. Williams . . 3494

Some Applications of Valence-bond Theory to Aromatic Substitution.
By A. L. Green 3538

Note :

A Base-catalysed Rearrangement, of Non-benzilic Acid Type, of a Bridged α-Diketone.
By R. H. Burnell and W. I. Taylor 3636

Organic.

Simple Analogues of Cortisone. Part III. Some Monocyclic Compounds.
By J. D. Billimoria and N. F. Maclagan 3257

Some Derivatives of Tetra- and Hexa-hydro-4 : 6-dioxopyrimidine.
By W. R. Boon, H. C. Carrington, N. Greenhalgh, and C. H. Vasey . . 3263

The Oxidation of Alkyl Sulphides.
By D. Edwards and J. B. Stenlake 3272

The Degradation of Carbohydrates by Alkali. Part VI. Laminaribiose and Turanose.
By W. M. Corbett and J. Kenner 3274

The Degradation of Carbohydrates by Alkali. Part VII. 5-*O*-Benzyl- and 2 : 5-*O*-Benzylidene-2-deoxy-D-ribose.
By J. Kenner and G. N. Richards 3277

The Degradation of Carbohydrates by Alkali. Part VIII. Melibiose.
By W. M. Corbett and J. Kenner 3281

2-Mercaptoglyoxalines. Part VIII. The Preparation of 2-Mercaptoglyoxalines from Glutamic Acid.
By R. A. F. Bullerwell, Alexander Lawson, and H. V. Morley . . . 3283

Triazoles. Part III. Mono- and Di-methyl(phenyl)-1 : 2 : 4-triazoles.
By M. R. Atkinson and J. B. Polya 3319

The Oxidation of Phenylhydrazones. Part IV.
By B. M. Lynch and K. H. Pausacker 3340

The Components of Wool Wax. Part II. Synthesis of the Acids and Alcohols of the *iso*- and the (+)-*anteiso*-Series.
By A. H. Milburn and E. V. Truter 3344

Homolytic Aromatic Substitution. Part VII. Partial Rate Factors for the Phenylation of *tert.*-Butylbenzene and *p*-Di-*tert.*-butylbenzene.
By J. I. G. Cadogan, D. H. Hey, and Gareth H. Williams 3352

Reactions of α-Halogeno-ketones with Aromatic Compounds. Part I. Reactions of Chloroacetone and 3-Chlorobutanone with Phenol and its Ethers.
By S. Husain Zaheer, Baldev Singh, Bharat Bhushan, P. M. Bhargava, I. K. Kacker, K. Ramachandran, V. D. N. Sastri, and N. Shanmukha Rao . . 3360

The Decarboxylative Acylation of Succinic Acid Derivatives. Part I. Benzamidosuccinic Acid.
By Alexander Lawson 3363

Deoxy-sugars. Part XXV. Structure and Reactivity of Anhydro-sugars. Part II. Derivatives of 3 : 6-Anhydro-D-mannose, 3 : 6-Anhydro-2-deoxy-D-galactose, and 3 : 6-Anhydro-2-deoxy-D-glucose.
By A. B. Foster, W. G. Overend, M. Stacey, and G. Vaughan . . . 3367

αβ-Unsaturated Aldehydes and Related Compounds. Part V. Reaction of Acraldehyde with Simple Aliphatic Alcohols. Formation of Acraldehyde Dialkyl Acetals and of β-Alkoxypropaldehydes and their Acetals.
By R. H. Hall and E. S. Stern 3388

The Synthesis of Isotopically Labelled Adenosine-2′ Phosphate and Adenosine-3′ Phosphate.
By G. R. Barker 3396

Experiments on the Synthesis of Lysergic Acid. Part I. Derivatives of Indole.
By J. A. Barltrop and D. A. H. Taylor 3399

PAGE

Experiments on the Synthesis of Lysergic Acid. Part II. Derivatives of 1-Azaphenanthrene.
By J. A. BARLTROP and D. A. H. TAYLOR 3403

The Mechanism for the Conversions of Uric Acid into Allantoin and Glycine.
By C. E. DALGLIESH and A. NEUBERGER 3407

The Oxidation of Monoethenoid Fatty Acids and Esters. Catalytic Oxidation of *n*-Propyl Oleate. The Oxidation Products.
By A. J. FEUELL and J. H. SKELLON 3414

Steroids and Walden Inversion. Part XV. The Mechanism and Stereochemical Course of Some Grignard Carboxylations and Oxygenations.
By G. ROBERTS and C. W. SHOPPEE 3418

Steroids. Part VIII. 3 : 5-*cyclo*Ergosta-7 : 9(11) : 22-trien-6β-ol (*i*-Dehydroergosterol).
By R. W. REES and C. W. SHOPPEE 3422

Cyclic Amidines. Part I. Derivatives of Phenhomazine (Dibenzo[*b*, *f*]-1 : 5-diazocine).
By F. C. COOPER and M. W. PARTRIDGE 3429

Studies in Stereochemical Structure. Part XI. Heterocyclic Compounds from Benzoin.
By ROBERT ROGER, KENNETH C. REID, and ROBERT WOOD 3453

1 : 2 : 4-Triazoles. Part I. A Synthesis of 3 : 5-Disubstituted 1 : 2 : 4-Triazoles.
By K. T. POTTS 3461

The Optical Resolution and Racemisation of Some Di*iso*quinolyls.
By MALCOLM CRAWFORD and I. F. B. SMYTH 3464

Infra-red Spectra of Carbohydrates. Part II. Anomeric Configuration of Some Hexo- and Pento-pyranoses.
By S. A. BARKER, E. J. BOURNE, R. STEPHENS, and D. H. WHIFFEN . . . 3468

The Alkaloids of *Picralima nitida*, Stapf, Th. and H. Durand. Part I. The Structure of Akuammigine.
By SIR ROBERT ROBINSON and A. F. THOMAS 3479

Branched-chain Thia-alkanebis(quaternary Ammonium) Salts as Ganglion-blocking Agents.
By K. J. M. ANDREWS, F. BERGEL, and A. L. MORRISON 3483

Ring Expansion. Part I. The Dienone–Phenol Rearrangement of *spiro*[5 : 5]Undeca-1 : 4-dien-3-one.
By R. H. BURNELL and W. I. TAYLOR 3486

*cyclo*Octatetraene Derivatives. Part VI. Preparation of Barbituric Acids.
By W. O. JONES and D. S. WITHEY 3490

Sesquiterpenoids. Part IV. The Constitution of Carissone.
By D. H. R. BARTON and E. J. TARLTON 3492

The Addition of Isoprene to 4-Methoxytoluquinone.
By W. A. AYER, L. G. HUMBER, and W. I. TAYLOR 3505

The Thermal Decomposition of Octyl Nitrite in Hydrocarbon Solvents.
By BERNARD A. GINGRAS and WILLIAM A. WATERS 3508

Steroids and Walden Inversion. Part XVI. The Epimeric Cholestan-7-ols.
By R. J. W. CREMLYN and C. W. SHOPPEE 3515

Cereal Gums. Part I. The Methylation of Barley Glucosans.
By G. O. ASPINALL and R. G. J. TELFER 3519

The Alkaloids of *Picralima nitida*, Stapf, Th. and H. Durand. Part II. Some Investigations concerning the Structure of *pseudo*Akuammigine.
By SIR ROBERT ROBINSON and A. F. THOMAS 3522

α-1 : 4-Glucosans. Part II. The Molecular Structure of the Liver Glycogen from a Case of von Gierke's Disease.
By D. J. MANNERS 3527

Bisbenzyl*iso*quinolines. Part I. The Synthesis of 4-(2-Aminoethyl)-5′-carboxymethyl-2 : 2′-dimethoxydiphenyl Ether and Phenoxy*iso*quinolines.
By M. F. GRUNDON and (in part) H. J. H. PERRY 3531

Hydrogen Transfer. Part I. Introductory Survey.
By E. A. BRAUDE and R. P. LINSTEAD 3544

Hydrogen Transfer. Part II. The Dehydrogenation of 1 : 4-Dihydronaphthalene by Quinones. Kinetics and Mechanism.
By E. A. BRAUDE, L. M. JACKMAN, and R. P. LINSTEAD 3548

PAGE

Hydrogen Transfer. Part III. The Dehydrogenation of Hydroaromatic Hydrocarbons by Quinones. Quantitative Comparison of Donors.
By E. A. BRAUDE, L. M. JACKMAN, and R. P. LINSTEAD 3564

Hydrogen Transfer. Part IV. The Use of Quinones of High Potential as Dehydrogenation Reagents.
By E. A. BRAUDE, A. G. BROOK, and R. P. LINSTEAD 3569

Hydrogen Transfer. Part V. Dehydrogenation Reactions with Diphenylpicrylhydrazyl.
By E. A. BRAUDE, A. G. BROOK, and R. P. LINSTEAD 3574

Hydrogen Transfer. Part VI. Metal-catalysed Transfer-hydrogenation of Ethylenic Compounds.
By E. A. BRAUDE, R. P. LINSTEAD, and P. W. D. MITCHELL 3578

Hydrogen Transfer. Part VII. Metal-catalysed Transfer-hydrogenation of Nitrocompounds.
By E. A. BRAUDE, R. P. LINSTEAD, and K. R. H. WOOLDRIDGE 3586

Hydrogen Transfer. Part VIII. Metal-catalysed Transfer-hydrogenation of Miscellaneous Acceptors.
By E. A. BRAUDE, R. P. LINSTEAD, P. W. D. MITCHELL, and K. R. H. WOOLDRIDGE 3595

Organometallic and Organometalloidal Fluorine Compounds. Part X. Trifluoromethylphosphonous and -phosphonic Acids.
By F. W. BENNETT, H. J. EMELÉUS, and R. N. HASZELDINE 3598

Chebulinic Acid. Part II.
By R. D. HAWORTH and L. B. DE SILVA 3611

Chebulinic Acid. Part III. Oxidation of Ellagic and Flavellagic Acids and the Synthesis of Some *iso*Coumarin Derivatives.
By R. D. HAWORTH, H. K. PINDRED, and (in part) P. R. JEFFERIES . . . 3617

Structure and Reactivity of Anhydro-sugars. Part III. An Interpretation of Some Reactions of 3 : 6-Anhydro-D-hexoses.
By A. B. FOSTER, W. G. OVEREND, and G. VAUGHAN 3625

Deoxy-sugars. Part XXVI. The Cleavage of Sulphonic Esters with Lithium Aluminium Hydride.
By R. ALLERTON and W. G. OVEREND 3629

NOTES :

Deoxy-sugars. Part XXVII. The Catalytic Oxidation of Some Derivatives of 2-Deoxy-D-hexoses.
By W. G. OVEREND, F. SHAFIZADEH, M. STACEY, and G. VAUGHAN . . . 3633

Solubility and Chromatography of Hydroxybenzoic Acids.
By P. A. ONGLEY 3634

The Preparation of 2-Deoxy-D-ribose.
By G. N. RICHARDS 3638

Preparation of *neo*Pentyl Chloride.
By W. GERRARD and P. TOLCHER 3640

Crystalline 1-Benzoyl-1 : 2-dihydroquinoline.
By R. F. COLLINS 3641

Preparation of ωω′-Diphenylpolymethylenes by Anodic Syntheses.
By E. A. EVANS and MARGARET WHALLEY 3642

The Synthesis of Sugars from Smaller Fragments. Part VIII. The Synthesis of D-*ido*-Heptulosan from D-Xylose.
By J. K. N. JONES 3643

INDEX OF AUTHORS' NAMES.

ALLERTON, R., and Overend, W. G., 3629.
Anbar, M., Dostrovsky, I., Samuel, D., and Yoffe, A. D., 3603.
Anderson, J. S., Edgington, D. N., Roberts, L. E. J., and Wait, E., 3324.
Andrews, K. J. M., Bergel, F., and Morrison, A. L., 3483.
Aspinall, G. O., and Telfer, R. G. J., 3519.
Atkinson, M. R., and Polya, J. B., 3319.
Ayer, W. A., Humber, L. G., and Taylor, W. I., 3505.
Ayscough, P. B., and Emeléus, H. J., 3381.
Barker, G. R., 3396.
Barker, S. A., Bourne, E. J., Stephens, R., and Whiffen, D. H., 3468.
Barltrop, J. A., and Taylor, D. A. H., 3399, 3403.
Barton, D. H. R., and Tarlton, E. J., 3492.
Bennett, F. W., Emeléus, H. J., and Haszeldine, R. N., 3598.
Bergel, F. See Andrews, K. J. M., 3483.
Bhargava, P. M. See Zaheer, S. H., 3360.
Bhushan, B. See Zaheer, S. H., 3360.
Billimoria, J. D., and Maclagan, N. F., 3257.
Boon, W. R., Carrington, H. C., Greenhalgh, N., and Vasey, C. H., 3263.
Bourne, E. J. See Barker, S. A., 3468.
Bowen, H. J. M., 3637.
Bradley, D. C., Saad, M. A., and Wardlaw, W., 3488.
Braude, E. A., Brook, A. G., and Linstead, R. P., 3569, 3574.
Braude, E. A., Jackman, L. M., and Linstead, R. P., 3548, 3564.
Braude, E. A., and Linstead, R. P., 3544.
Braude, E. A., Linstead, R. P., and Mitchell, P. W. D., 3578.
Braude, E. A., Linstead, R. P., Mitchell, P. W. D., and Wooldridge, K. R. H., 3595.
Braude, E. A., Linstead, R. P., and Wooldridge, K. R. H., 3586.
Brook, A. G. See Braude, E. A., 3569, 3574.
Bullerwell, R. A. F., Lawson, A., and Morley, H. V., 3283.
Burnell, R. H., and Taylor, W. I., 3486, 3636.
Cadogan, J. I. G., Hey, D. H., and Williams, G. H., 3352.
Carrington, H. C. See Boon, W. R., 3263.
Collins, R. F., 3641.
Cooper, F. C., and Partridge, M. W., 3429.
Corbett, W. M., and Kenner, J., 3274, 3281.
Cottrell, T. L., and Graham, T. E., 3644.
Crawford, M., and Smyth, I. F. B., 3464.
Cremlyn, R. J. W., and Shoppee, C. W., 3515.
Dalgliesh, C. E., and Neuberger, A., 3407.
Davies, A. G., Kenyon, J., Lyons, B. J., and Rohan, T. A., 3474.
Dawson, J. K., 3393.
de Silva, L. B. See Haworth, R. D., 3611.
Dostrovsky, I. See Anbar, M., 3603.
Edgington, D. N. See Anderson, J. S., 3324.
Edwards, D., and Stenlake, J. B., 3272.
Emeléus, H. J. See Ayscough, P. B., 3381, and Bennett, F. W., 3598.
Evans, E. A., and Whalley, M., 3642.
Ferrett, D. J. See Irving, H., 3494.
Feuell, A. J., and Skellon, J. H., 3414.
Foster, A. B., Overend, W. G., Stacey, M., and Vaughan, G. 3367.
Foster, A. B., Overend, W. G., and Vaughan, G., 3625.
Gerrard, W., and Tolcher, P., 3640.
Gingras, B. A., and Waters, W. A., 3508.
Graham, T. E. See Cottrell, T. L., 3644.
Green, A. L., 3538.
Greenhalgh, N. See Boon, W. R., 3263.
Griffiths, J. H., and Phillips, C. S. G., 3446.
Grundon, M. F., and Perry, H. J. H., 3531.
Hall, R. H., and Stern, E. S., 3388.
Harnik, E., Herbstein, F. H., Schmidt, G. M. J., and Hirshfeld, F. L., 3288.
Harnik, E., and Schmidt, G. M. J., 3295.
Haszeldine, R. N. See Bennett, F. W., 3598.
Haworth, R. D., and de Silva, L. B., 3611.
Haworth, R. D., Pindred, H. K., and Jefferies, P. R., 3617.
Herbstein, F. H., and Schmidt, G. M. J., 3302, 3314.
Herbstein, F. H. See also Harnik, E., 3288.
Hetherington, G., and Robinson, P. L., 3512.
Hey, D. H. See Cadogan, J. I. G., 3352.
Hirshfeld, F. L. See Harnik, E., 3288.
Humber, L. G. See Ayer, W. A., 3505.
Irving, H., Williams, R. J. P., Ferrett, D. J., and Williams, A. E., 3494.
Jackman, L. M. See Braude, E. A., 3548, 3564.
Jefferies, P. R. See Haworth, R. D., 3617.
Johnstone, N. B. See Morrison, T. J., 3441.
Jones, J. K. N., 3643.
Jones, W. O., and Withey, D. S., 3490.
Kacker, I. K. See Zaheer, S. H., 3360.
Kenner, J., and Richards, G. N., 3277.
Kenner, J. See also Corbett, W. M., 3274, 3281.
Kenyon, J. See Davies, A. G., 3474.
Lawson, A., 3363.
Lawson, A. See also Bullerwell, R. A. F., 3283.
Leandri, G., and Tundo, A., 3377.
Linstead, R. P. See Braude, E. A., 3544, 3548, 3564, 3569, 3574, 3578, 3586, 3595.
Lynch, B. M., and Pausacker, K. H., 3340.
Lyons, B. J. See Davies, A. G., 3474.
Maclagan, N. F. See Billimoria, J. D., 3257.
McOmie, J. F. W. See Pollard, F. H., 3435.
Manners, D. J., 3527.
Milburn, A. H., and Truter, E. V., 3344.
Mitchell, P. W. D. See Braude, E. A., 3578, 3595.
Morley, H. V. See Bullerwell, R. A. F., 3283.
Morrison, A. L. See Andrews, K. J. M., 3483.
Morrison, T. J., and Johnstone, N. B., 3441.
Moser, C. M., 3455.
Neuberger, A. See Dalgliesh, C. E., 3407.
Ongley, P. A., 3634.
Overend, W. G., Shafizadeh, F., Stacey, M., and Vaughan, G., 3633.
Overend, W. G. See also Allerton, R., 3629, and Foster, A. B., 3367, 3625.
Partridge, M. W. See Cooper, F. C., 3429.
Pausacker, K. H. See Lynch, B. M., 3340.
Perry, H. J. H. See Grundon, M. F., 3531.
Phillips, C. S. G. See Griffiths, J. H., 3446.
Pindred, H. K. See Haworth, R. D., 3617.
Pollard, F. H., McOmie, J. F. W., and Stevens, H. M., 3435.
Polya, J. B. See Atkinson, M. R., 3319.
Potts, K. T., 3461.
Ramachandran, K. See Zaheer, S. H., 3360.
Rao, N. S. See Zaheer, S. H., 3360.

Rees, R. W., and Shoppee, C. W., **3422**.
Reid, K. C. See Roger, R., **3453**.
Richards, G. N., **3638**.
Richards, G. N. See also Kenner, J., **3277**.
Roberts, G., and Shoppee, C. W., **3418**.
Roberts, L. E. J., **3332**.
Roberts, L. E. J. See also Anderson, J. S., **3324**.
Robinson, P. L. See Hetherington, G., **3512**.
Robinson, Sir R., and Thomas, A. F., **3479**, **3522**.
Roger, R., Reid, K. C., and Wood, R., **3453**.
Rohan, T. A. See Davies, A. G., **3474**.
Saad, M. A. See Bradley, D. C., **3488**.
Samuel, D. See Anbar, M., **3603**.
Sastri, V. D. N. See Zaheer, S. H., **3360**.
Schmidt, G. M. J. See Harnik, E., **3288**, **3295**, and Herbstein, F. H., **3302**, **3314**.
Shafizadeh, F. See Overend, W. G., **3633**.
Shoppee, C. W. See Cremlyn, R. J. W., **3515**, Rees, R. W., **3422**, and Roberts, G., **3418**.
Singh, B. See Zaheer, S. H., **3360**.
Skellon, J. H. See Feuell, A. J., **3414**.
Smyth, I. F. B. See Crawford, M., **3464**.
Stacey, M. See Foster, A. B., **3367**, and Overend, W. G., **3633**.
Stenlake, J. B. See Edwards, D., **3272**.
Stephens, R. See Barker, S. A., **3468**.
Stern, E. S. See Hall, R. H., **3388**.
Stevens, H. M. See Pollard, F. H., **3435**.
Tarlton, E. J. See Barton, D. H. R., **3492**.
Taylor, D. A. H. See Barltrop, J. A., **3399**, **3403**.
Taylor, W. I. See Ayer, W. A., **3505**, and Burnell, R. H., **3486**, **3636**.
Telfer, R. G. J. See Aspinall, G. O., **3519**.
Thomas, A. F. See Robinson, Sir R., **3479**, **3522**.
Tolcher, P. See Gerrard, W., **3640**.
Truter, E. V. See Milburn, A. H., **3344**.
Tundo, A. See Leandri, G., **3377**.
Vasey, C. H. See Boon, W. R., **3263**.
Vaughan, G. See Foster, A. B., **3367**, **3625**, and Overend, W. G., **3633**.
Wait, E. See Anderson, J. S., **3324**.
Wardlaw, W. See Bradley, D. C., **3488**.
Waters, W. A. See Gingras, B. A., **3508**.
Whalley, M. See Evans, E. A., **3642**.
Whiffen, D. H. See Barker, S. A., **3468**.
Williams, A. E. See Irving, H., **3494**.
Williams, G. H. See Cadogan, J. I. G., **3352**.
Williams, R. J. P. See Irving, H., **3494**.
Winter, E. R. S., **3342**.
Withey, D. S. See Jones, W. O., **3490**.
Wood, R. See Roger, R., **3453**.
Wooldridge, K. R. H. See Braude, E. A., **3586**, **3595**.
Yoffe, A. D. See Anbar, M., **3603**.
Zaheer, S. H., Singh, B., Bhushan, B., Bhargava, P. M., Kacker, I. K., Ramachandran, K., Sastri, V. D. N., and Rao, N. S., **3360**.

NOTICES TO AUTHORS OF PAPERS

Scientific communications for the *Journal* should be addressed to " The Honorary Secretaries, The Chemical Society, Burlington House, London, W.1." Papers to be read before a meeting of the Society are selected by the Honorary Secretaries.

A paper is not normally considered for publication in the *Journal* unless at least one of the authors is a Fellow of the Society, but in exceptional circumstances the Council is prepared to consider papers submitted by non-Fellows.

Communications that have appeared or have been accepted for publication with essentially the same scientific content in another Journal or freely available printed work shall not be published in the *Journal* of the Society unless this course is approved by the Council.

Papers are accepted by the Society on the understanding that the authors have obtained any necessary authority to publish.

The Society reserves the right to retain all papers sent to it, and authors are therefore advised to keep copies. When papers have been accepted for publication the authors are not at liberty, save by permission of the Council, to withdraw or delay them, or to publish them elsewhere until they have appeared in the *Journal* of the Society. Papers which are retained by the Council after being judged unsuitable for publication in the *Journal* are deposited in the Archives of the Society; this right is not usually exercised in regard to illustrations.

Authors are solely responsible for the factual accuracy of their papers. They are particularly requested to verify references.

Authors are requested to see that their papers conform, as nearly as possible, to the normal conventions of the *Journal*. It is essential that drawings and photographs be presented in the style required by the Society. Every paper must be prefaced by a short summary, but " Notes " do not require a summary. Authors should consult the brochure entitled " The Presentation of Papers for the Journal of the Chemical Society " for detailed instructions and advice on these and cognate matters; Fellows of the Society are entitled to one copy each, gratis, on application to the General Secretary, The Chemical Society, Burlington House, London, W.1; further copies may be obtained at the public price which is 1*s.* 6*d.* each, post free, or 12*s.* 6*d.* per 10 copies, post free.

Authors are expected to be familiar with the normal rules of nomenclature, but are invited to communicate with the Editor if in doubt or in special cases. Some of the principles followed are reviewed in " Modern Chemical Nomenclature," by Dr. Clarence Smith (*J.*, 1936, 1067) (6*d.* post free), and in the Editorial Reports on Nomenclature (*J.*, 1950, 3699; 1951, 3515; 1952, 5057) (1*s.* each post free). Much valuable discussion will be found in " British Chemical Nomenclature," by Dr. A. D. Mitchell [Edward Arnold and Co., 1948]. Authors should choose their symbols from the " Report by the Symbols Committee of the Royal Society representing the Royal Society, the Chemical Society, the Faraday Society, and the Physical Society, 1951 " (*J.*, 1951, 1677) [9*d.* per copy or 12*s.* per 25 copies (post free), obtainable from the General Secretary, The Chemical Society].

Authors will be expected to pay the cost of any considerable changes made by them in proof, apart from the correction of printers' errors.

Each author, or joint author, receives 10 preprints (without covers) free of charge. A quotation for extra preprints and an order form will be sent with the proofs. The order form (and any necessary remittance) must be returned with the proofs and the MS. to the Editor.

INFORMATION FOR CANDIDATES FOR FELLOWSHIP

The Chemical Society was founded in 1841 and received a Royal Charter in 1848.

The main function of the Society is to foster original research in chemistry and to facilitate the discussion and dissemination of new knowledge in all branches of the science.

Fellowship of the Society is open to men and women of all nationalities who are interested in chemistry and wish to keep in touch with its advances. Fellows are elected by the Council.

PRIVILEGES

Fellows paying the Annual Subscription of £4 10*s*. have the following privileges:

To receive a selection of the publications of the Society to a value of £3 0*s*. without further payment.

To purchase additional publications at favourable prices.

To attend all meetings, discussions and lectures of the Society and to introduce two guests.

To consult and borrow books in the Library. Books may be borrowed by post.

To apply for grants from the Research Fund.

To submit papers for publication in the *Journal*.

Fellows under 27 years of age may pay £1 15*s*. per annum and receive:

The *Proceedings*, *Annual Reports on the Progress of Chemistry*, and *Quarterly Reviews* without further payment.

The right to purchase other publications at favourable prices.

All the other privileges of Fellowship.

LIBRARY

The extensive reference and lending library of the Chemical Society contains over 50,000 volumes dealing with every aspect of chemistry and with many branches of related sciences. The library is open on Monday to Friday from 10 a.m. to 9 p.m., and on Saturdays from 10 a.m. to 5 p.m.

Books available on loan may be sent by post to Fellows residing in Great Britain or Ireland.

MEETINGS

(*a*) *In London.*—Scientific Meetings of the Society are usually held on two Thursdays in each month from October to June at Burlington House, at which papers dealing with original work are read and discussed, organised discussions on subjects of current interest are arranged, and lectures by eminent British and foreign chemists are delivered.

(*b*) *Outside London.*—Scientific Meetings and lectures arranged by the Society's Local Representatives are also held outside London, and form an important part of the activities of the Society.

RESEARCH FUND

A Research Fund is available for the assistance of chemical research, and sums amounting annually to about £700 are granted for this purpose. Application for grants must be made on the appropriate form, which may be obtained from the General Secretary.

A brochure describing the activities of the Society and forms of application for Fellowship can be obtained from THE GENERAL SECRETARY, THE CHEMICAL SOCIETY, BURLINGTON HOUSE, PICCADILLY, LONDON, W.1.

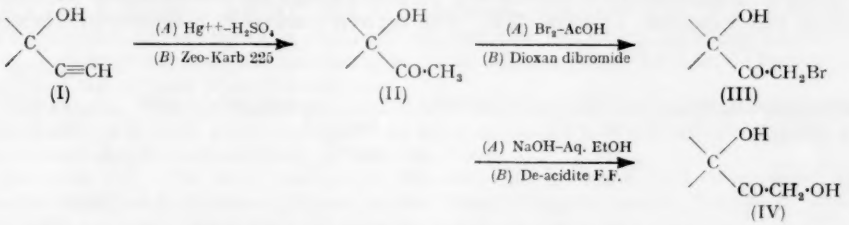
Simple Analogues of Cortisone. Part III. Some Monocyclic Compounds.*

By J. D. Billimoria and N. F. Maclagan.

[Reprint Order No. 5274.]

The hydration of some ethynylcarbinols (I) to acetylcarbinols (II) has been catalysed by an acid ion-exchange resin (Zeo-Karb 225) impregnated with mercuric ions. Bromination of (II) with dioxan dibromide has yielded the bromoacetylcarbinols (III). A basic ion-exchange resin (De-acidite F.F.) has been found to hydrolyse the α-keto-bromides (III) very smoothly to the glycolloylcarbinols (IV). Thus, 1-glycolloyl*cyclo*heptanol, 1-glycolloyl-4-methyl*cyclo*hexanol, 1-glycolloyl-3-methyl*cyclo*hexanol and 1-glycolloyl-2 : 2-dimethyl*cyclo*hexanol have been prepared. 1-Glycolloyl*cyclo*heptanol showed slight biological activity in the mouse-liver glycogen test.

In view of a slight but significant biological activity shown by (*sol.*)-1-glycolloyl-2-methyl-*cyclo*hexanol * in the liver glycogen test (see below), we have prepared some more simple alicyclic compounds incorporating the dihydroxy-acetone moiety of cortisone.



The general scheme shown above has been used; some of the transformations (I) to (IV) were carried out by previously used reagents (marked *A*) and others by new ones (marked *B*).

Newman (*J. Amer. Chem. Soc.*, 1953, **75**, 4740) hydrated 1-ethynyl*cyclo*hexanol to 1-acetyl*cyclo*hexanol by using the ion-exchange resin Dowex-50 previously impregnated with 1% mercuric sulphate. We have independently found the resin Zeo-Karb 225 (a polystyrenesulphonic acid), impregnated with 1% mercuric ions, very effective in hydrating 1-ethynyl*cyclo*hexanol. With 1-ethynyl-2-methyl*cyclo*hexanol, however, pretreatment of the resin with 20% mercuric sulphate was necessary, and 1-acetyl-2-methyl*cyclo*hexanol was then rapidly obtained in excellent yield. Other ethynyl compounds were equally readily hydrated by use of this resin.

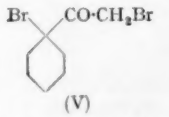
The bromination of acetylcarbinols (II) (Part I, *J.*, 1951, 3067), previously regarded as an acid-catalysed reaction, has now been carried out by treating their ethereal solutions with an equivalent of dioxan dibromide (Yanosskaya, Terent'ev, and Belen'kii, *Zhur. Obshchey Khim.*, 1952, **22**, 1594; *Chem. Abs.*, 1953, **47**, 8032) and irradiating the mixture with strong visible light. Anhydrous conditions were maintained by preparing the dioxan dibromide in light petroleum.

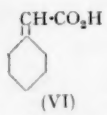
Wagner and Moore (*J. Amer. Chem. Soc.*, 1950, **72**, 1874) hydrolysed the dibromide (V) with aqueous potassium carbonate and found that, although a large portion was rearranged to the acid (VI), about 20% was converted into the required ketol (VII; R = H).

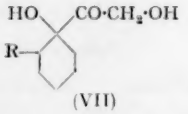
Similar treatment of (*sol.*)-1-bromoacetyl-2-methyl*cyclo*hexanol (VIII) failed, the unchanged bromide being recovered as a pyridinium adduct. The hydrolyses of such α-keto-bromides, a major obstacle in our route for the introduction of the keto-alcohol side-chain into simple compounds, has now been overcome by the use of the basic ion-exchange resin De-acidite F.F. Thus, the bromide (VIII), treated in hot methanol with De-acidite F.F., gave the keto-alcohol (VII; R = Me) in high yield.

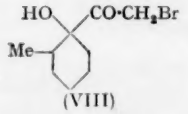
* Part II, *J.*, 1953, 2626.

1-Ethynyl*cyclo*heptanol was hydrated with aqueous sulphuric acid–mercuric sulphate, or by the ion-exchange process, to 1-acetyl*cyclo*heptanol in 60% and 85% yields, respectively. Conversion into 1-bromoacetyl*cyclo*heptanol followed by hydrolysis yielded


(V)


(VI)


(VII)

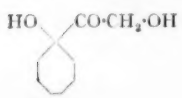

(VIII)

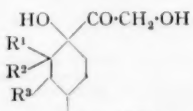
1-glycolloyl*cyclo*heptanol (IX). The latter readily reduced alkaline copper sulphate and furnished a semicarbazone.

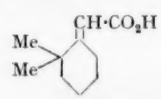
1-Ethynyl-4-methyl*cyclo*hexanol formed an unstable mercury complex during the sulphuric acid hydration, but was smoothly converted into 1-acetyl-4-methyl*cyclo*hexanol by the ion-exchange process. This ketone when irradiated in ether in the presence of dioxan dibromide gave 1-bromoacetyl-4-methyl*cyclo*hexanol which when refluxed with aqueous methanol and De-acidite F.F. yielded 1-glycolloyl-4-methyl*cyclo*hexanol (X; $R^1 = R^2 = R^3 = H$, $R^4 = Me$).

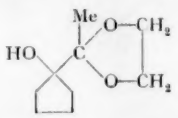
Similarly, 1-ethynyl-3-methyl*cyclo*hexanol gave a liquid 1-glycolloyl-3-methyl*cyclo*hexanol (X; $R^1 = R^2 = R^4 = H$, $R^3 = Me$).

Crude 2 : 2-dimethyl*cyclo*hexanone was purified through its semicarbazone (Adamson, Marlow, and Simonsen, *J.*, 1938, 774). The derived 1-acetyl-2 : 2-dimethyl*cyclo*hexanol


(IX)


(X)


(XI)


(XII)

furnished a crystalline 1-bromoacetyl-2 : 2-dimethyl*cyclo*hexanol, which on hydrolysis with aqueous ethanolic sodium hydroxide, followed by chromatography (alumina), gave only a trace of a keto-alcohol. This gave analytical data agreeing with formulation as 1-glycolloyl-2 : 2-dimethyl*cyclo*hexanol (X; $R^1 = R^2 = Me$, $R^3 = R^4 = H$) and reduced alkaline copper sulphate, but the quantity was insufficient for characterisation. An acid, probably the rearranged acid [XI (?), cf. Wagner and Moore, *loc. cit.*], was also isolated from the hydrolysate.

Ethynylation of *cyclo*pentanone with sodium acetylide in liquid ammonia gave poor yields of 1-ethynyl*cyclo*pentanol, due mainly to the formation of *cyclo*pentylidene*cyclo*pentanone. Hydration of the ethynylcarbinol by the sulphuric acid–mercuric sulphate method was unsatisfactory. Better results were obtained when 1-ethynyl*cyclo*pentanol and ethylene glycol reacted in the presence of a boron trifluoride–ether complex–mercuric oxide catalyst. The ketal (XII) was thus obtained in 60% yield from which the parent acetyl-carbinol was readily obtained by mild acid hydrolysis. Hydration of the ethynylcarbinol with Zeo-Karb 225–mercuric ion catalyst, however, gave directly 1-acetyl*cyclo*pentanol in 80% yield. Some modifications in the methods of ethynylation of *cyclo*pentanone and the hydration of the acetylenic alcohol with mercuric sulphate, leading to better yields, have been reported since the completion of this work (Stacey and Mikulie, *J. Amer. Chem. Soc.*, 1954, **76**, 525).

Infra-red spectra * of 1-glycolloyl*cyclo*heptanol and 1-glycolloyl-4-methyl*cyclo*hexanol show the following absorption bands (in $cm.^{-1}$; % absorption in parentheses) :

	C=O	Ring OH	Ketol-OH
1-Glycolloyl*cyclo*heptanol	1710 (95)	3250 (92)	2900 (85)
1-Glycolloyl-4-methyl*cyclo*hexanol	1710 (65)	3100—3175 (80)	2900 (70)

* These will appear in Sadtler's " Catalogue of Infra-red Spectrograms," Philadelphia. They were determined on a Baird double-beam instrument, that of 1-glycollolyl-4-methyl*cyclo*hexanol as a film from chloroform and that of 1-glycollolyl*cyclo*heptanol in 10% solution in chloroform.

Biological Activity.—Three of the compounds referred to were tested for adrenocortical activity by the mouse-liver glycogen method described below with the following results:

Compound	Dosage, g./kg.	No. of mice	Liver glycogen, mg./100 g. bodyweight, control	test	Significance
1-Glycolloyl*cyclo*heptanol	1	16	12·6 ± 1·4	34·5 ± 5·4	P = 0·001
1-Glycolloyl-2-methyl*cyclo*hexanol	0·7	19	14·4 ± 1·6	22·2 ± 3·0	P = 0·02—0·05
1-Glycolloyl-4-methyl*cyclo*hexanol	1	21	24·9 ± 3·5	17·5 ± 3·0	none

It will be seen that two compounds displayed a small but significant activity at high dosages. Control tests with equivalent doses of dihydroxyacetone gave negative results indicating that this activity was not due to direct conversion of the compounds into carbohydrate.

Experimental

The microanalyses were carried out in the Microanalytical Laboratory, Organic Chemistry Department, Imperial College of Science and Technology (Mr. F. H. Oliver) and by Dr. Sobotka, University of Graz.

Preparation of the Resins.—Zeo-Karb 225–mercuric ion. The damp Zeo-Karb 225 (British Permutit; mesh 200—400; 1000 g.) was suspended in a column (3″ diam.) and washed under suction with hydrochloric acid (4 l.; 10% w./v.) followed by distilled water (8 l.). After being dried in air (2 days), and then in a vacuum at 50°, the resin (200 g.) was vigorously shaken with 2N-aqueous sulphuric acid (2 l.) containing mercuric sulphate (40 g.) for 1 hr. The resin was filtered off and air-dried (2 days) before use.

Regeneration. The spent resin was washed with ether, ethanol, and water and stirred with aqueous nitric acid (25% w./v.) for 2 days. It was then washed with acid and water, dried, and impregnated with mercuric sulphate, as described above.

De-acidite F.F. The damp resin (mesh 200—400; 250 g.) was washed on a column with 2N-aqueous sodium hydroxide (2 l.) and distilled water (4 l.), and vacuum dried at 60° before use. After use it was regenerated with 2N-aqueous sodium hydroxide.

Dioxan Dibromide.—Bromine (320 g.) was added with vigorous hand stirring to dioxan (160 g.; distilled over sodium), and the warm solution (*ca.* 60°) was poured into light petroleum (2 l.; b. p. <40°), precooled to −20°. The yellow precipitate was filtered off under suction and freed from solvent under vacuum as rapidly as possible (there is a considerable loss due to volatility of the dibromide). The compound, m. p. 60—61°, was used without further purification and could be stored at 0°.

1-*Acetyl*cyclo*heptanol.—Method* A. To an aqueous sulphuric acid solution (140 c.c. of acid and 1300 c.c. of water) of mercuric sulphate (52 g.) was added with stirring a solution of 1-ethynyl-*cyclo*heptanol (240 g.) in carbon tetrachloride (500 c.c.), the temperature being maintained below 25°. The white precipitate first formed decomposed to an oil after 2 hours' stirring. The organic layer was separated and the mother liquor extracted with carbon tetrachloride (2 × 250 c.c.). The combined extracts were run into mercuric sulphate (15 g.), sulphuric acid (80 c.c.), and water (625 c.c.) under steam distillation. From the distillate, after extraction (carbon tetrachloride) and distillation, 1-*acetyl*cyclo*heptanol* was obtained (163 g., 60%), b. p. 100—101°/9 mm., n_D^{21} 1·4765 (Found: C, 69·1; H, 10·5. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%). The *semicarbazone*, prepared in aqueous pyridine, crystallised from ethanol in needles, m. p. 198° (Found: C, 56·1; H, 8·9; N, 19·4. $C_{10}H_{19}O_2N_3$ requires C, 56·2; H, 8·9; N, 19·7%).

Method B. A solution of ethynyl*cyclo*heptanol (100 g.) in methanol (250 c.c.) and water (70 c.c.) was refluxed with stirring and Zeo-Karb 225–mercuric ion resin (25 g.) added. (After 1 hr. a test portion of filtered reaction mixture gave no precipitation with ammoniacal silver nitrate. A second portion with aqueous silver nitrate was only weakly acid to universal-indicator paper, showing absence of the acetylenic group.) The solution was refluxed for a further 1 hr. Removal of the resin by filtration, evaporation of solvent, and distillation of the residue gave 1-acetyl*cyclo*heptanol (91 g., 80%), n_D^{21} 1·4766 (Found: C, 69·1; H, 10·3%). This gave a semicarbazone, m. p. 198° (undepressed when melted in admixture with the material prepared by method A).

1-*Bromoacetyl*cyclo*heptanol.—Method* A. 1-Acetyl*cyclo*heptanol (100 g.) in acetic acid (100 c.c.) was treated with bromine (34 c.c.) in acetic acid containing hydrogen bromide (0·25 g.). After 6 min., the bromine was decolorised with evolution of hydrogen bromide. The solution

was poured on crushed ice and extracted with ether, and the extract was neutralised ($NaHCO_3$), dried (Na_2SO_4), and distilled, giving 1-*bromoacetylcycloheptanol* (100 g.), b. p. 75°/10^{-5} mm. (evaporative distillation; bath temp. 100—110°), n_D^{21} 1·5150 (Found: Br, 33·7. $C_9H_{15}O_2Br$ requires Br, 34·0%).

1-*Glycolloylcycloheptanol.*—*Method* A. 1-Bromoacetylcycloheptanol (110 g.), dissolved in ethanol (360 c.c.) and water (240 c.c.), was treated with a solution of sodium hydroxide (18·8 g.) in aqueous ethanol (300 c.c.; 60% w./v.) added in portions (25 c.c.) with vigorous shaking. Subsequent additions were made only after each portion of the alkali was neutralised (phenolphthalein). The solution was evaporated in vacuum (50°) and the residual oil was dissolved in ether and dried (Na_2SO_4). The ether was distilled off and the residue crystallised from ether (sodium dried; 70 c.c.) by cooling to −40°. After the crystals (19 g.) had been filtered off, the filtrate on dilution with light petroleum (b. p. <40°) deposited a further crop (2 g.), m. p. 58—59°. Sublimation in high vacuum followed by crystallisation from ether–light petroleum (b. p. 40—60°) yielded 1-*glycolloylcycloheptanol* (19 g.) as plates, m. p. 62—63° (Found: C, 62·7; H, 9·3. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%).

1-*Ethynyl-4-methylcyclohexanol.*—This alcohol (110 g., 80%) was obtained by the reaction of 4-methylcyclohexanone (112 g.) with sodium acetylide (from sodium, 24 g.) in liquid ammonia (2 l.). After distillation, the product was obtained as a crystalline mass, m. p. 15—24°. Laborious fractional crystallisation of a small portion from light petroleum (b. p. 40—60°) gave a trace of a pure *isomer*, m. p. 36° (Found: C, 78·1; H, 10·1. $C_9H_{14}O$ requires C, 78·3; H, 10·1%). For further work the mixture, m. p. 15—24°, was used.

1-*Acetyl-4-methylcyclohexanol.*—*Method* B. 1-Ethynyl-4-methylcyclohexanol (100 g.), Zeo-Karb 225–mercuric ion (25 g.), methanol (300 c.c.), and water (70 c.c.) were refluxed with stirring for 2 hr. The mixture was worked up as previously described giving the ketone (92 g., 80%), b. p. 90—95°/10 mm. The semicarbazone, formed in aqueous pyridine, was crystallised from ethanol to constant m. p. 181—182°. This appeared to be homogenous and on regeneration with warm aqueous sulphuric acid gave a pure isomer of 1-*acetyl-4-methylcyclohexanol* (64 g.), b. p. 99—100°/10 mm. (Found: C, 69·5; H, 10·2. $C_9H_{16}O_2$ requires C, 69·3; H, 10·3%). The *semicarbazone* of this ketone, without further crystallisation, had m. p. 182—183° (Found: C, 56·5; H, 9·0; N, 20·0. $C_{10}H_{19}O_2N_3$ requires C, 56·3; H, 8·9; N, 19·7%)

1-*Bromoacetyl-4-methylcyclohexanol.*—*Method* B. 1-Acetyl-4-methylcyclohexanol (31·2 g.) in dry ether (50 c.c.) was added to dioxan dibromide (50 g.) in ether (500 c.c.). The red solution was irradiated with a 250-watt G.E.C. lamp; after 3 min. the ether was colourless and a small quantity of red oil separated. On further irradiation (2—3 min.) the solution was again homogeneous and colourless. The mixture was rapidly washed with water and dried (Na_2SO_4), and 1-*bromoacetyl-4-methylcyclohexanol* was obtained, by evaporative distillation, as a pale yellow liquid (38 g.), b. p. 75—80°/10^{-6} mm. (bath temp. 100—110°) (Found: Br, 34·1. $C_9H_{15}O_2Br$ requires Br, 34·0%).

Pyridinium adduct. The bromide (3 g.; not distilled), anhydrous ether (100 c.c.), and pyridine (5 c.c.) were kept at 0° for 24 hr., an oil separating. The ether was decanted off, and the residue, on trituration with chloroform and light petroleum (40—60°), solidified. A solution of the solid in cold methanol (2 c.c.) was diluted with ether and kept at 0°, the *pyridinium* adduct (4 g.) then separating in needles, m. p. 194—195° (Found: C, 53·4; H, 6·5; N, 4·5; Br, 25·2. $C_{14}H_{20}O_2NBr$ requires C, 53·5; H, 6·3; N, 4·5; Br, 25·4%).

1-*Glycolloyl-4-methylcyclohexanol.*—*Method* B. The bromide (20 g.), De-acidite F.F. (50 g.), methanol (350 c.c.), and water (100 c.c.) were refluxed with vigorous stirring (20 hr.). The resin was filtered off, and the filtrate concentrated under vacuum (<60°). The residual oil was dissolved in ether and dried (Na_2SO_4); removal of the solvent followed by crystallisation from light petroleum (b. p. 40—60°) containing a little ether, gave 1-*glycolloyl-4-methylcyclohexanol* (8 g.) as plates, m. p. 80—81° (Found: C, 63·1; H, 9·4. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%). The compound deposited cuprous oxide when heated on the water-bath with Somogyi's reagent, and further addition of Nelson's arsenomolybdate reagent to this mixture gave a dark blue solution (Somogyi, *J. Biol. Chem.*, 1945, **160**, 61; Nelson, *J. Biol. Chem.*, 1944, **153**, 375).

1-Ethynyl-3-methylcyclohexanol (100 g.), prepared in 80% yield by the sodium acetylide–liquid ammonia method, was suspended in light petroleum and stirred with a solution (2 l.) of aqueous ammoniacal silver nitrate (containing 125 g. of silver nitrate). The mixture was kept for 12 hr. at 0°, and the silver salt filtered off, washed with ether, suspended in light petroleum (b. p. 80—100°), and shaken with a solution (3 l.) of saturated aqueous ammonium thiocyanate. The regenerated acetylenic carbinol had b. p. 56—60°/1 mm., n_D^{25} 1·4702. At 0—5° it crystallised

in fine needles but was liquid at room temperature (Found : C, 78·5; H, 10·1. Calc. for $C_9H_{14}O$: C, 78·3; H, 10·1%). (Rupe and Kambli, *Annalen*, 1927, **459**, 195, give two isomers, one of m. p. 55° and the other a liquid. The present compound was essentially the liquid isomer.)

1-*Acetyl*-3-*methyl*cyclo*hexanol*.—*Method* A. The acetylenic carbinol (200 g.) was hydrated with mercuric sulphate (52·5 g.) in aqueous sulphuric acid (140 c.c. of H_2SO_4; 1200 of c.c. H_2O). The mercury complex was decomposed by steam distillation as previously described, 1-*acetyl*-3-*methyl*cyclo*hexanol* (140 g.) being obtained, b. p. 68°/1 mm., n_D^{21} 1·4641 (Found : C, 69·1; H, 10·5. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%). The ketone was converted into the *semicarbazone*, needles (from methanol), m. p. 211—212° (Found : C, 56·6; H, 9·2; N, 19·5. $C_{10}H_{19}O_2N_3$ requires C, 56·3; H, 8·9; N, 19·7%).

1-*Bromoacetyl*-3-*methyl*cyclo*hexanol*.—*Method* A The above ketone (31 g ; regenerated from the semicarbazone), dissolved in chloroform (20 c.c.) was added to a solution of bromine (32 g.), hydrogen bromide (0·25 g.), and acetic acid (0·5 c.c.) in chloroform (200 c.c.). After 20 min., the solution became colourless, and it was worked up in the usual manner, 1-*bromoacetyl*-3-*methyl*cyclo*hexanol* (29 g.), b. p. 75°/10^{-6} mm., being obtained by evaporative distillation. The bromide was too labile to be analysed and a portion was characterised as the *pyridinium* adduct, crystallising from dry methanol–ether in needles, m. p. 172—173° (Found : C, 53·2; H, 6·4; N, 4·3; Br, 25·5. $C_{14}H_{20}O_2NBr$ requires C, 53·5; H, 6·3; N, 4·5; Br, 25·4%).

1-*Glycolloyl*-3-*methyl*cyclo*hexanol*.—*Method* A. The bromoacetyl compound (20 g.) in ethanol (150 c.c.) and water (60 c.c.) was titrated as previously described with sodium hydroxide (3·5 g.) in aqueous ethanol (100 c.c.; 60% w./v.). The solvents were removed *in vacuo* (below 50°) and the *keto-alcohol* (6 g.), b. p. 60°/10^{-6} mm., n_D^{20} 1·4921 (Found : C, 62·4; H, 9·1. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%), obtained by evaporative distillation. The *thiosemicarbazone* separated from methanol as pale yellow needles, m. p. 208° (decomp.) (Found : C, 49·0; H, 7·8; N, 17·2; S, 13·0. $C_{10}H_{19}O_2N_3S$ requires C, 49·0; H, 7·8; N, 17·1; S, 13·2%).

(*sol.*)-1-*Acetyl*-2-*methyl*cyclo*hexanol*.—*Method* B. The hydration of (*sol.*)-1-ethynyl-2-methyl*cyclo*hexanol (100 g.) with Zeo-Karb 225–mercuric ions (25 g.) in aqueous methanol (350 c.c.; 70% w./v.) yielded (*sol.*)-1-acetyl-2-methyl*cyclo*hexanol (92 g.), m. p. 36° undepressed when melted on admixture with a previously prepared sample (Part II, *loc. cit.*).

(sol.)-1-*Bromoacetyl*-2-*methyl*cyclo*hexanol*.—*Method* B. When the ketone (15·6 g.) was brominated with dioxan dibromide (25 g.) in ether (200 c.c.), there was obtained the bromide, m. p. 62—63° undepressed on admixture with a previously prepared sample (Part II).

(sol.)-1-*Glycolloyl*-2-*methyl*cyclo*hexanol*.—*Method* B. The bromide (7·8 g.), De-acidite F.F. (15 g.), and aqueous methanol (300 c.c.) were heated under reflux (20 hr.) The hydroxy-ketol (3·9 g.), isolated in the usual manner, had m. p. 81—82° undepressed on admixture with an authentic specimen (Part II).

1-*Acetyl*-2 : 2-*dimethyl*cyclo*hexanol*.—Crude 2 : 2-dimethyl*cyclo*hexanone semicarbazone was fractionally crystallised from methanol to constant m. p. 199—200° (Adamson, Marlow, Simonsen, *loc. cit.*). 2 : 2-Dimethyl*cyclo*hexanone (126 g.), regenerated from this semicarbazone, gave with sodium acetylide (39 g.), 1-ethynyl-2 : 2-dimethyl*cyclo*hexanol (120 g.), b. p. 78°/6 mm., n_D^{22} 1·4788 (Found : C, 78·5; H, 10·9. Calc. for $C_{10}H_{16}O$: C, 78·9; H, 10·5%). The acetylenic alcohol (100 g.) was converted with mercuric sulphate (27 g.) and aqueous sulphuric acid (70 c.c. of H_2SO_4 and 600 c.c. of H_2O) into 1-*acetyl*-2 : 2-*dimethyl*cyclo*hexanol* (80 g.), b. p. 101°/8 mm., n_D^{21} 1·4733 (Found : C, 70·5; H, 10·8. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·6%). The *semicarbazone* separated from ethanol as cubes, m. p. 204—205° (Found : C, 58·4; H, 9·2; N, 18·6. $C_{11}H_{21}O_2N_3$ requires C, 58·2; H, 9·3; N, 18·5%).

1-*Bromoacetyl*-2 : 2-*dimethyl*cyclo*hexanol*.—*Method* A. 1-Acetyl-2 : 2-dimethyl*cyclo*hexanol (17 g.) was brominated in chloroform (170 c.c.) with bromine (16·2 g.) containing hydrogen bromide (0·25 g.) and acetic acid (5 c.c.). On distillation, the bromide had b. p. 80°/10^{-6} mm., and solidified on cooling to 0°. 1-*Bromoacetyl*-2 : 2-*dimethyl*cyclo*hexanol* crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 65° (Found : C, 48·3; H, 6·8; Br, 32·3. $C_{10}H_{17}O_2Br$ requires C, 48·2; H, 6·8; Br, 32·1%).

Hydrolysis of the bromide. The bromide (14 g.) in aqueous ethanol (60% w./v.; 100 c.c.) was neutralised with sodium hydroxide (2·3 g.) in aqueous ethanol (60% w./v.; 100 c.c.). The solution was concentrated under reduced pressure and water (50 c.c.) added. The solution was extracted into ether, the two layers separated, and the ether layer dried (Na_2SO_4). (*a*) The ether extract, after removal of solvent, left an oil which was dissolved in a minimum of light petroleum (b. p. 40—60°)–ether and chromatographed on alumina (nitrogen atmosphere). A portion eluted with light petroleum (b. p. 40—60°), twice crystallised from the same solvent, gave only a trace of the *hydroxy-ketol* as needles, m. p. 56° (Found : C, 64·1; H, 9·3. $C_{10}H_{18}O_3$

requires C, 64·5; H, 9·6%). The compound readily reduced the Somoygi reagent and gave a deep blue colour with the Nelson reagent (*loc. cit.*).

(*b*) The aqueous layer was acidified and extracted into ether. Purification of the acid gave, after evaporation of the solvent, an oily residue which eventually solidified. Crystallisation from hot aqueous acetic acid gave 2 : 2-*dimethyl*cyclo*hexylideneacetic acid* (?) as a dihydrate, m. p. 70° (indefinite) (Found : C, 59·2; H, 9·5. $C_{10}H_{16}O_2,2H_2O$ requires C, 58·8; H, 9·8%). On dehydration at 100° in vacuum it had m. p. 145—146° (Found : C, 71·1; H, 9·3. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·5%). This compound readily decolorised aqueous acidified potassium permanganate.

*Ethynyl*cyclo*pentanol and* cyclo*Pentylidene*cyclo*pentanone*.—Sodium acetylide, from sodamide (195 g.) in liquid ammonia (5 l.), was treated with *cyclo*pentanone (420 g.) in the usual manner. Distillation yielded 1-ethynyl*cyclo*pentanol (280 g.), b. p. 52—54°/2 mm., m. p. *ca.* 20°. A higher-boiling fraction (b. p. 60—90°/2 mm.; 130 g.) on refractionation gave *cyclo*pentylidene*cyclo*pentanone, b. p. 119°/8 mm., $n_D^{20\cdot5}$ 1·5220 (Found : C, 79·8; H, 10·5. Calc. for $C_{10}H_{14}O$: C, 80·0; H, 10·6%). The compound decolorised acidified potassium permanganate.

1-*Acetyl*cyclo*pentanol*.—1-Ethynyl*cyclo*pentanol (100 g.), Zeo-Karb 225–mercuric ion (25 g.), and aqueous methanol (70% w./v.; 300 c.c.) were refluxed (2 hr.) with stirring. Filtration followed by distillation of the filtrate gave 1-acetyl*cyclo*pentanol, b. p. 71—74°/11 mm., n_D^{20} 1·4650 (Found : C, 65·4; H, 9·1. Calc. for $C_7H_{12}O_2$: C, 65·6; H, 9·3%). The semicarbazone had m. p. 185—186° (Found : C, 57·7; H, 8·1; N, 23·0. $C_8H_{15}O_2N_3$ requires C, 57·9; H, 8·1; N, 22·7%). Both compounds were identical with previously prepared specimens (Billimoria and Maclagan, *J.*, 1951, 3067. The m. p. of the semicarbazone was erroneously reported as 206—208°).

2-1′-*Hydroxy*cyclo*pentyl*-2-*methyl*-1 : 3-*dioxolan*.—Mercuric oxide (4·5 g.) was covered with freshly distilled boron trifluoride–ether complex (2 c.c.) and dried ethylene glycol (5 g.). The mixture was warmed for a few minutes and then externally cooled, whilst a mixture of ethylene glycol (20 g.) and 1-ethynyl*cyclo*pentanol (35 g.) was run in dropwise with stirring. After the addition, the mixture was stirred (1·5—2 hr.), and then left overnight. Next day, anhydrous potassium carbonate (5 g.) was added and the solution stirred for a few minutes. The liquid was separated by centrifugation and distilled through a 6″ Vigreux column. The *ketal* (34 g.) was obtained as a viscous liquid, b. p. 69—70°/1 mm. (bath temp. 100°), $n_D^{23\cdot5}$ 1·4695 (Found : C, 62·5; H, 9·1. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%).

Hydrolysis. A portion of the ketal dissolved in a little methanol containing a few c.c. of aqueous 5% hydrochloric acid was warmed on the water-bath for 20 min. Addition of an excess of pyridine followed by the addition of semicarbazide hydrochloride gave the semicarbazone of 1-acetyl*cyclo*pentanol; this had m. p. and mixed m. p. 185—186°.

Biological Assay.—Groups of thirty mice (each 18—20 g.) were adrenalectomised on Day 1 and kept at 23° ± 1°. 8—10 animals were used for each of the control and the experimental groups. Drugs or control vehicle (arachis oil) were injected on the evening of Day 3 and again on the morning of Day 4. At 4 p.m. on Day 4 the animals were killed and the glycogen content of the livers was estimated by a slightly modified version of Venning, Kazmin, and Bell's method (*Endocrinol.*, 1946, **38**, 79).

We are indebted to the Empire Rheumatism Council and the Governors' Discretionary Fund, Westminster Hospital, for generous financial assistance, to Miss Patricia Maxwell for technical assistance, and to Samuel P. Sadtler & Son Inc., Philadelphia, for the infra-red spectra. We gratefully acknowledge the assistance of Mr. A. J. Feetham in the biological testing of the compounds.

Department of Chemical Pathology,
Westminster Medical School, London, S.W.1.

[*Received, April 2nd*, 1954.]

Some Derivatives of Tetra- and Hexa-hydro-4 : 6-dioxopyrimidine.

By W. R. Boon, H. C. Carrington, N. Greenhalgh, and C. H. Vasey.

[Reprint Order No. 5313.]

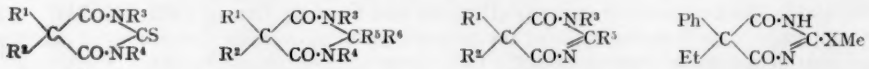
Hydrogenolysis of 5 : 5-di-, and 1 : 3 : 5- and 1 : 5 : 5-tri-, and 1 : 3 : 5 : 5-tetra-substituted 2-thiobarbituric acids in alcohol gives, according to the conditions, hexahydro-4 : 6-dioxopyrimidines or the corresponding 2-alkoxy-derivatives. The transformations of these substances and further methods for their synthesis are described.

Carrington, Vasey, and Waring (*J.*, 1953, 3105) prepared a number of di- and tetra-hydro-oxoglyoxalines by hydrogenolysis of the corresponding monothiohydantoin derivatives with Raney nickel. A related pyrimidine derivative, 5-ethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine ("Mysoline," primidone) (II; $R^1 = Ph$, $R^2 = Et$, $R^3 = R^4 = R^5 = R^6 = H$) is an effective anticonvulsant, both in the control of experimentally induced convulsions in laboratory animals (Bogue and Carrington, *Brit. J. Pharmacol.*, 1953, **8**, 230) and in the treatment of epilepsy (Handley and Stewart, *Lancet*, 1952, **242**, 742). The present paper describes methods for the preparation of pyrimidine derivatives of this type, and considers some of their reactions. Only those compounds are recorded here which are important in illustrating the chemistry of this group of substances. Others are described in B.P. 666,027 and in pending Applications.

The synthetical methods fall into two classes. In the first class, reduction of barbituric acids or their 2-thio-derivatives leads to the hexahydrodioxopyrimidines themselves, or, in some cases where alcohols are used as solvents, to 2-alkoxy-derivatives which are converted on further reduction into the hexahydrodioxopyrimidines. In the second class are methods in which malonic acid derivatives react with carboxylic acids or their derivatives; a special case is the reaction of *C*-disubstituted malonodiamides with formic acid or formamide, leading directly to the hexahydrodioxopyrimidines; the other methods of this class, in which various malonic acid derivatives (chlorides, esters, amides, etc.) react with amidines, esters, acid chlorides, etc., vary widely in their usefulness, but they all lead first to the tetrahydrodioxopyrimidines, or to the related 2-alkoxy-compounds, from which the hexahydro-compounds are obtained by reduction; and, in some cases, they are adaptable to the synthesis of 2-alkyl derivatives.

Only one other member of this series (II; $R^1 = R^2 = Et$, $R^3 = R^4 = R^5 = R^6 = H$) has been described previously. It was obtained by Tafel and Thompson (*Ber.*, 1907, **40**, 4491) by electrolytic reduction of barbitone and by Einhorn and Diesbach (*ibid.*, p. 4902; *Annalen*, 1908, **359**, 171) by reduction of 5 : 5-diethyl-2-thiobarbituric acid with sodium amalgam. Primidone was first prepared by hydrogenolysis of 5-ethyl-5-phenyl-2-thiobarbituric acid with the W5 Raney nickel of Adkins and Billica (*J. Amer. Chem. Soc.*, 1948, **70**, 695). Sodium amalgam, or zinc and formic acid, could also be used, and electrolytic reduction of phenobarbitone itself gave the same product. Hydrogenolysis of a 5 : 5-disubstituted 2-thiobarbituric acid is a satisfactory general method for the preparation of hexahydro-4 : 6-dioxopyrimidines (II; $R^5 = R^6 = H$), including those in which R^3 and/or R^4 are alkyl. In contrast, hydrogenolysis of 5-phenyl-2-thiobarbituric acid (I; $R^1 = Ph$, $R^2 = R^3 = R^4 = H$) gave only 4 : 6-dihydroxy-5-phenylpyrimidine (Hull, *J.*, 1951, 2214), while that of the 1 : 3-dimethyl-5-phenyl analogue (I; $R^1 = Ph$, $R^3 = R^4 = Me$, $R^2 = H$) proceeded normally to give the hexahydropyrimidine (II; $R^1 = Ph$, $R^3 = R^4 = Me$, $R^2 = R^5 = R^6 = H$), presumably because in the former case the intermediate tetrahydro-compound is a tautomer of the aromatic dihydroxy-compound, which resists further reduction, while in the latter an aromatic structure is impossible. The only other restrictions on the use of the hydrogenolysis procedure appear to be that the substituents in the thiobarbituric acid must not be sensitive to reduction by Raney nickel; *e.g.*, hydrogenolysis of the *cyclo*hex-1-enyl compound (I; $R^1 = C_6H_9$, $R^2 = Et$, $R^3 = R^4 = H$) gave, as main product, the *cyclo*hexyl compound (II; $R^1 = C_6H_{11}$, $R^2 = Et$, $R^3 = R^4 = R^5 = R^6 = H$); and under similar conditions primidone was obtained from the *o*-, *m*-, or *p*-chlorophenyl compound (I; $R^1 = C_6H_4Cl$, $R^2 = Et$, $R^3 = R^4 = H$).

When the hydrogenolysis was effected in methanol or ethanol solution with W1 Raney nickel (Adkins and Pavlic, *ibid.*, 1947, **69**, 3039), which contains less adsorbed hydrogen than the W5 type, or with Raney cobalt, prepared as W5 nickel, the products were 2-alkoxyhexahydro-4 : 6-dioxopyrimidines, *e.g.*, (I; R^1 = Ph, R^2 = Et, $R^3 = R^4$ = H) gave (II; R^1 = Ph, R^2 = Et, $R^3 = R^4 = R^5$ = H, R^6 = OMe or OEt); in *n*- or *iso*-propanol the hexahydropyrimidines (II; $R^5 = R^6$ = H) were obtained. Similarly 5-ethyl-1 : 3-dimethyl-5-phenyl-2-thiobarbituric acid (I; R^1 = Ph, R^2 = Et, $R^3 = R^4$ = Me) gave the 2-methoxy-compound (II) on hydrogenolysis in methanol. By contrast, hydrogenolysis of 5-ethyltetrahydro-2-methoxy(or methylthio)-4 : 6-dioxo-5-phenylpyrimidine (IV; X = O or S) with W1 Raney nickel or Raney cobalt gave primidone. The assignment of the alkoxyhexahydropyrimidine structure to substances such as (II; R^1 = Ph, R^2 = Et, $R^3 = R^4 = R^5$ = H) is based, first, on their reaction with formaldehyde to give bishydroxymethyl derivatives (*e.g.*: II; R^1 = Ph, R^2 = Et, $R^3 = R^4 = CH_2{\cdot}OH$, R^5 = H, R^6 = OMe) and, secondly, on the existence of similar alkoxy-compounds when $R^3 = R^4$ = alkyl, the alternative alcoholate structure being then impossible.



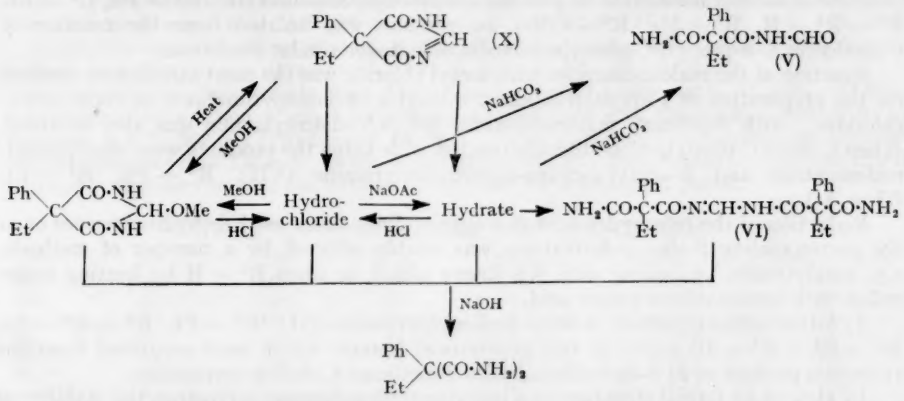
(I) (II) (III) (IV)

The main transformations of the 2-alkoxyhexahydro-4 : 6-dioxopyrimidines are well exemplified by the behaviour of (II; R^1 = Ph, R^2 = Et, $R^3 = R^4 = R^5$ = H, R^6 = OMe). It was unchanged on crystallisation from any alcoholic solvent examined but lost methanol at 180° in a high vacuum to give the tetrahydropyrimidine (III; R^1 = Ph, R^2 = Et, $R^3 = R^5$ = H) which, although it could not be purified satisfactorily, regenerated the starting material on crystallisation from methanol and, with other alcohols gave the corresponding 2-alkoxy-derivatives. When heated above 200° the 2-alkoxy-derivatives gave insoluble, infusible polymers. With ethereal hydrogen chloride the 2-alkoxy-derivatives gave the hydrochloride of the tetrahydro-compound, which was converted into the hydrate of the latter in sodium acetate solution, but into *C*-ethyl-*N*-formyl-*C*-phenylmalonodiamide (V) in sodium hydrogen carbonate solution. With alcohols both the hydrate and the hydrochloride gave the 2-alkoxy-derivatives. The hydrate with boiling water gave *NN'*-di-(α-carbamoyl-α-phenylbutyryl)formamidine (VI), converted by further heating into *C*-ethyl-*C*-phenylmalonodiamide.

Compounds of type (II) in which R^5 = alkyl, and R^6 = OAlkyl, are somewhat less stable than when R^5 = H; it was also not possible to obtain derivatives in which R^6 was other than OMe, or occasionally OEt. 5-Ethylhexahydro-2-methoxy-4 : 6-dioxo-5-phenylpyrimidine (II; R^1 = Ph, R^2 = Et, $R^3 = R^4 = R^5$ = H, R^6 = OMe), and the corresponding tetrahydro-compound (III; R^1 = Ph, R^2 = Et, $R^3 = R^5$ = H) and its hydrochloride and hydrate, as well as *C*-ethyl-*N*-formyl-*C*-phenylmalonodiamide (V) and the corresponding bis-compound (VI), gave *C*-ethyl-*C*-phenylmalondiamide with cold dilute sodium hydroxide solution.

For the second class of syntheses, the most promising method would formally be the condensation of a derivative of malonodiamide with formaldehyde or of a malonyl chloride or malonic ester with methylenediamine. Einhorn (*Annalen*, 1905, **343**, 207) reported a number of unsuccessful attempts to prepare the hexahydro-compound (II; $R^1 = R^2$ = Et, $R^3 = R^4 = R^5 = R^6$ = H) by reaction of diethylmalonyl chloride with methylenediamine and of *CC*-diethylmalonodiamide with formaldehyde. Many attempts to synthesise primidone on these lines were unsuccessful. *C*-Ethyl-*C*-phenylmalondiamide and formaldehyde gave smoothly a bishydroxymethyl compound but attempts to convert this into a mono(hydroxymethyl) derivative directly, or to effect cyclisation, were fruitless. However *C*-ethyl-*C*-phenylmalondiamide with boiling formamide or with formic acid at a high temperature gave primidone smoothly; and this reaction was generally applicable to *CC*-disubstituted malonodiamides and their *N*-monosubstituted derivatives. From *C*-ethyl-*C*-phenyl-*N*-*iso*propylmalonodiamide and formamide the only product was primidone. A similar, though usually incomplete, amide interchange was always observed

with derivatives of *C*-methyl-*C*-phenylmalonodiamide. Heating *CC*-diphenylmalonodiamide with formamide caused gross decomposition if the reaction period were prolonged; the monosubstituted malonodiamide (IX; R^1 = Ph, R^2 = H) was converted into phenylacetamide. There is little doubt that the cyclisation reaction proceeds *via* the *N*-formylmalonodiamide which then cyclises, with loss of water, to the tetrahydropyrimidine, which is, in turn, reduced by the excess of formic acid or formamide. The intermediate compounds have never been isolated from the reaction mixture, apparently because the last



stage occurs at a lower temperature than the earlier ones. Thus, 5-ethyltetrahydro-4 : 6-dioxo-5-phenylpyrimidine is rapidly reduced by boiling formic acid, which hydrolyses *C*-ethyl-*N*-formyl-*C*-phenylmalonodiamide to the parent diamide. The requisite malonodiamides were prepared by treating the malonyl chlorides with ammonia, or more conveniently by hydrolysis of the corresponding cyanoacetamides with concentrated sulphuric acid. The latter method was less satisfactory with α-cyano-α-phenyl-*N*-*iso*propylbutyramide (VII; R^1 = Ph, R^2 = Et, R^3 = Pr^i), from which *C*-ethyl-*C*-phenylmalonodiamide and *C*-ethyl-*C*-phenyl-*NN'*-di*iso*propylmalonodiamide were obtained in addition to a small amount of the expected product; a possible explanation is that propylene is eliminated and then, in the form of *iso*propyl hydrogen sulphate, reacts with the nitrile (cf. Benson and Ritter, *J. Amer. Chem. Soc.*, 1949, **71**, 4128) The method failed with (VII; R^1 = Ph, R^2 = Et, R^3 = CH_2Ph, or CH_2:$CH{\cdot}CH_2$), only sulphonated water-soluble products being obtained.

$R^1R^2C(CN){\cdot}CO{\cdot}NHR^3$ (VII) Me·NH·CO·CPhEt·CO·N:CH·NH·CO·CPhEt·CO·NHMe (VIII) $R^1R^2C(CO{\cdot}NH_2)_2$ (IX)

All the other methods of synthesis of hexahydro-4 : 6-dioxopyrimidines which have been employed involve the intermediate isolation of a tetrahydro-4 : 6-dioxopyrimidine, or the corresponding 2-alkoxyhexahydro-4 : 6-dioxopyrimidine. These methods can be used for the preparation of 2-alkyl-derivatives. Freund and Fleischer (*Annalen*, 1910, **379**, 30) prepared the 2-methyl derivative (III; R^1 = R^2 = Et, R^3 = R^4 = R^6 = H, R^5 = Me) from diethylmalonyl chloride and an excess of acetamide. The same product is obtained (B.P. Appln. 17,043/1947) by the condensation of ethyl diethylmalonate with acetamidine. Freund and Fleischer's method failed when applied to ethylphenylmalonyl chloride. Condensation of ethyl ethylphenylmalonate with propionamidine in presence of sodium methoxide occurred readily at 105—110°, to give the hexahydro-2-methoxy-derivative (II; R^1 = Ph, R^2 = R^5 = Et, R^3 = R^4 = H, R^6 = OMe); with acetamidine under similar conditions the yield was very much poorer, while with formamidine the product (II; R^1 = Ph, R^2 = Et, R^3 = R^4 = R^5 = H, R^6 = OMe) was obtained only by prolonged reaction at 0—10°.

Condensation of *C*-ethyl-*C*-phenylmalondiamide with ethyl formate in presence of

sodium methoxide gave (II; R^1 = Ph, R^2 = Et, R^3 = R^4 = R^5 = H), also obtained by reaction of (V) with sodium methoxide. Condensation of a *C*-disubstituted malonodiamide (IX) with ethyl formate appeared to be a general reaction, but substitution on the amide-nitrogen atom prevented ring closure. Thus *C*-ethyl-*N*-methyl-*C*-phenylmalonodiamide gave as the only identifiable product *NN'*-di-(α-methylcarbamoyl-α-phenylbutyryl)-formamidine (VIII).

Although *C*-ethyl-*C*-phenylmalonodiamide condensed smoothly with ethyl acetate in presence of sodium methoxide to give the 2-methoxy-compound (II; R^1 = Ph, R^2 = Et, R^3 = R^4 = H, R^5 = Me, R^6 = OMe), no product was isolated from the reaction of *C*-methyl(or *C*-*n*-propyl)-*C*-phenylmalonodiamide under similar conditions.

Reaction of the malonodiamides with acetyl chloride was the most satisfactory method for the preparation of 1-alkyltetrahydro-2-methyl-4 : 6-dioxopyrimidines, as their hydrochlorides; with diprimary malonodiamides the *NN'*-diacetylamide was also obtained. When *C*-ethyl-*C*-phenylmalonodiamide reacted with keten the products were ethylphenylmalononitrile and *N*-acetyl-α-cyano-α-phenylbutyramide (VII; R^1 = Ph, R^2 = Et, R^3 = Ac).

Reduction of the tetrahydro-4 : 6-dioxopyrimidines either as their hydrochlorides or as the corresponding 2-alkoxy-derivatives was readily effected by a number of methods, *e.g.*, catalytically, by boiling with W5 Raney nickel, or when R^5 = H by heating under reflux with formamide or formic acid.

2 : 5-Diethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine (II; R^1 = Ph, R^2 = R^5 = Et, R^3 = R^4 = R^6 = H) exists in two geometrical isomers which were separated from the reduction product of 2 : 5-diethylhexahydro-2-methoxy-4 : 6-dioxopyrimidine.

In view of its formal structure as a diacylmethylenediamine derivative, the stability of primidone is noteworthy. It was unchanged on boiling with 5% hydrochloric acid or 2N-sodium hydroxide. Boiling 60% w/w sulphuric acid liberated formaldehyde. Oxidation with alkaline permanganate gave *C*-ethyl-*C*-phenylmalonodiamide. Primidone could not be methylated by means of methyl sulphate in alkali; on the other hand, 1 : 3-dimethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine (II; R^1 = Ph, R^2 = R^5 = R^6 = H, R^3 = R^4 = Me) was readily methylated by this reagent at position 5.

Primidone is readily nitrated to the 3'-nitro-derivative, whose constitution was determined by conversion into the 3'-chloro-derivative, identical with that synthesised from *m*-chlorotoluene. During the reduction of the nitro-compound some azoxy-derivative was obtained, as well as the amine. In addition to undergoing the Sandmeyer reaction, this amine was readily methylated to the dimethylamino-derivative and the trimethylammonium iodide, and was converted into the hydroxy-compound and thence by methyl sulphate and alkali into the methoxy-derivative.

The fact that primidone gave the 3'-nitro-derivative appeared, at first sight, surprising, since Bourquet and Adams (*J. Amer. Chem. Soc.*, 1930, **52**, 224) suggested that nitration of phenobarbitone gave the 4'-nitro-compound which was converted into the corresponding chloro-compound. Repetition of this work, however, showed that the product was 5-*m*-chlorophenyl-5-ethylbarbituric acid identical with the product obtained from *C*-*m*-chlorophenyl-*C*-ethylmalonodiamide and diethyl carbonate. Bourquet and Adams based their assignment of the structure on the fact that nitration of diethyl ethylphenylmalonate gives predominantly, the *p*-nitro-compound.

Since this work was completed our attention has been drawn to the paper by Staněk and Sidle (*Československá farmacie*, 1953, **2**, 117), describing the desulphurisation of a number of cyclic thioamides by Raney nickel.

Experimental

Ethyl m-*Chlorophenylacetate*.—3-Chlorobenzyl cyanide (76 g.) in absolute ethanol (210 c.c.) was saturated with dry hydrogen chloride at 0°. After 15 hr., the excess of solvent was removed under reduced pressure, the residual syrup was dissolved in ethanol (200 c.c.), and water (200 c.c.) was added. After 1 hr., the oil which separated was extracted with ether, dried ($MgSO_4$), and distilled, to give *ethyl* m-*chlorophenylacetate* (80 g.), b. p. 143°/6 mm. (Found: C, 60·4; H, 5·3. $C_{10}H_{11}O_2Cl$ requires C, 60·5; H, 5·55%).

Ethyl phenylpropylmalonate, b. p. 174°/20 mm. (Found : C, 69·4; H, 7·7. $C_{16}H_{22}O_4$ requires C, 69·0; H, 7·9%), was made in 93% yield by catalytic reduction of ethyl allylphenylmalonate over Adams platinum.

Ethyl m-*chlorophenylethylmalonate*, b. p. 184°/17 mm. (Found : C, 59·9; H, 6·3; Cl, 12·4. $C_{15}H_{19}O_4Cl$ requires C, 60·2; H, 6·4; Cl, 11·9%), and *ethyl* p-*chlorophenylethylmalonate*, b. p. 190—196°/18 mm. (Found : C, 60·7; H, 6·3; Cl, 12·4%), were prepared by substantially the method of Wallingford, Homeyer, and Jones (*J. Amer. Chem. Soc.*, 1941, **63**, 2056; cf. Wallingford, Thorpe, and Homeyer, *ibid.*, 1942, **64**, 580). By using an equivalent quantity of the appropriate benzyl cyanide (Wallingford, Jones, and Homeyer, *ibid.*, p. 576) were prepared *ethyl* α-m-, b. p. 177°/21 mm. (Found : C, 62·5; H, 5·8; N, 5·2; Cl, 14·8. $C_{13}H_{11}O_2NCl$ requires C, 62·0; H, 5·6; N, 5·6; Cl, 14·2%), and *ethyl* α-p-*chlorophenyl*-α-*cyanobutyrate*, b. p. 175°/20 mm. (Found : C, 62·3; H, 5·4; N, 5·2; Cl, 14·6%).

α-Cyano-α-phenylbutyramide, m. p. 117° (Found : N, 14·7. Calc. for $C_{11}H_{12}ON_2$: 14·9%), was obtained by reaction of ethyl α-cyano-α-phenylbutyrate with ammonia, substantially as described in G.P. 309,508 (Friedländer, **13**, 801). Other substituted *cyanoacetamides* prepared similarly are shown in Table 1. When a primary amine was used instead of ammonia it was frequently necessary to heat the mixture at 80—100° for a prolonged period.

TABLE 1. *Cyanoacetamides*, $R^1R^2C(CN)\cdot CO\cdot NHR^3$.

R^1	R^2	R^3	M. p.	Formula	Found : N, %	Reqd. : N, %
Ph	Me	H	107°	$C_{10}H_{10}ON_2$	16·3	16·1
Ph	Et	Me	73	$C_{12}H_{14}ON_2$	13·8	13·9
Ph	Et	Et	51	$C_{13}H_{16}ON_2$	12·9	13·0
Ph	Et	Pr^i	62	$C_{14}H_{18}ON_2$	12·2	12·2
Ph	Et	Allyl	*	$C_{14}H_{16}ON_2$	12·1	12·3
Ph	Et	CH_2Ph	81	$C_{18}H_{18}ON_2$	10·0	10·1
m-C_6H_4Cl	Et	H	108	$C_{11}H_{11}ON_2Cl$	12·9	12·6
p-C_6H_4Cl	Et	H	105	$C_{11}H_{11}ON_2Cl$	12·3	12·6

* B. p. 118°/0·4 mm.

CC-*Disubstituted Malonodiamides*.—These were made essentially by the method given in G.P. 310,426 (Friedländer, **13**, 802) for the preparation of ethylphenylmalonodiamide; in general, however, the reaction was effected at room temperature. Details of the various products are given in Table 2. Hydrolysis of α-cyano-α-phenyl-*N*-*iso*propylbutyramide gave, in addition to ethylphenyl-*N*-*iso*propylmalonodiamide, ethylphenylmalonodiamide and *ethylphenyl*-NN'-*di*iso*propylmalonodiamide*, m. p. 105° (from methanol) (Found : C, 70·4; H, 9·0; N, 9·6. $C_{17}H_{26}O_2N_2$ requires C, 70·3; H, 9·0; N, 9·7%), identical with material obtained from ethylphenylmalonyl chloride and *iso*propylamine. *Phenyl*-n-*propylmalonodiamide*, as well as some of the symmetrical diamides reported in Table 2, were made by treating the appropriate malonyl chloride with ice-cold aqueous ammonia. The malonyl chlorides were prepared by reaction of the acids with 2 mols. of phosphorus pentachloride, the acid being obtained in the usual way by hydrolysis of the diethyl ester. Neither the acids nor the chlorides were purified for analysis.

TABLE 2. *Malonodiamides*, $R^1R^2C(CO\cdot NH_2)\cdot CO\cdot NHR^3$.

R^1	R^2	R^3	M. p.	Formula	Found : N, %	Reqd. : N, %
Ph	Me	H	151°	$C_{10}H_{12}O_2N_2$	14·2	14·6
Ph	Et	Me	144	$C_{12}H_{16}O_2N_2$	12·5	12·7
Ph	Et	Et	127	$C_{13}H_{18}O_2N_2$	11·8	12·0
Ph	Pr^n	H	173	$C_{12}H_{16}O_2N_2$	12·3	12·7
Ph	Et	Pr^i	111	$C_{14}H_{20}O_2N_2$	11·4	11·3
m-C_6H_4Cl	Et	H	137	$C_{11}H_{13}O_2N_2Cl$	11·6	11·7
p-C_6H_4Cl	Et	H	138	$C_{11}H_{13}O_2N_2Cl$	11·3	11·7

C-*Ethyl*-NN'-*bishydroxymethyl*-C-*phenylmalonodiamide*.—*C*-Ethyl-*C*-phenylmalonodiamide (21 g.), 37% formaldehyde (28 c.c.), water (75 c.c.), and potassium carbonate (1 g.) were heated at 70° for 30 min. The solid which separated was extracted with boiling methanol, to give the *hydroxymethyl* derivative (10 g.), m. p. 188—189° (Found : C, 59·4; H, 6·7; N, 10·5. $C_{13}H_{18}O_4N_2$ requires C, 58·7; H, 6·8; N, 10·5%).

C-*Ethyl*-N-*formyl*-C-*phenylmalonodiamide*.—The above bishydroxymethyl derivative (10 g.) was added with shaking to potassium dichromate (30 g.) and sulphuric acid (25 g.) in water (150 c.c.) at 35—37°. After 3 hours' stirring at this temperature the white solid was filtered off and extracted with boiling acetone. Addition of water to the extract precipitated the *amide*,

m. p. 170° (from aqueous acetone) (Found: C, 61·1; H, 5·6; N, 12·1. $C_{12}H_{14}O_3N_2$ requires C, 61·5; H, 6·0; N, 12·0%).

Thiobarbituric Acids.—Two methods of preparation were employed: (a) *Condensation of an ethyl malonate with thiourea.* To a solution of sodium (46 g., 2 mol.) in methanol (700 c.c.), thiourea (74 g. 1 mol.) and the substituted ethyl malonate (1 mol.) were added. After 6 hours' heating under reflux the bulk of the solvent was removed under reduced pressure and the residual syrup was dissolved in ice-water. After removal of unchanged ester by extraction with ether, the thiobarbituric acid was precipitated by the addition of hydrochloric acid and crystallised from methanol. Details of the *products* are given in Table 3.

TABLE 3. *2-Thiobarbituric acids* (I).

R^1	R^2	R^3	R^4	M. p.	Formula	Found: N, %	Reqd.: N, %
Ph	H	H	H	264—267° *	$C_{10}H_8O_2N_2S$	12·0	12·7
Ph	H	Me	Me	220	$C_{12}H_{12}O_2N_2S$	11·2	11·3
Ph	Et	Me	H	125	$C_{13}H_{14}O_2N_2S$	10·5	10·7
Ph	Et	Me	Me	112	$C_{14}H_{16}O_2N_2S$	10·0	10·0
m-C_6H_4Cl	Et	H	H	167	$C_{12}H_{11}O_2N_2SCl$	9·9	9·9
p-C_6H_4Cl	Et	H	H	193	$C_{12}H_{11}O_2N_2SCl$	9·3	9·9
·CH_2·CH_2·CH_2·		H	H	365 *	$C_7H_8O_2N_2S$	15·1	15·2

* With decomp.

(b) *Reaction of a malonyl chloride with thiourea.* This method was preferred for the preparation of *N*-substituted thiobarbituric acids. The malonyl chloride (0·25 mol.) and the thiourea (0·42 mol.) were heated on the steam-bath for 9 hr., and the resulting mass was then crystallised from methanol. Ethylphenylmalonyl chloride and *N-iso*propylthiourea reacted abnormally, to give on crystallisation from methanol N-(α-*methoxycarbonyl*-α-*phenylbutyryl*)-N′-iso*propylthiourea*, m. p. 107° (Found: C, 59·5; H, 6·7; N, 8·9. $C_{16}H_{22}O_3N_2S$ requires C, 59·6; H, 6·8; N, 8·7%).

5-Ethyltetrahydro-2-methylthio-4 : *6-dioxo-5-phenylpyrimidine.*—5-Ethyl-5-phenyl-2-thiobarbituric acid (12·4 g.), methyl iodide (10 g.), methanol (150 c.c.), water (2 c.c.), and sodium hydroxide (2·2 g.) were mixed. After 15 hr. some solvent was removed under reduced pressure, the oily layer was taken up in ether and dried ($MgSO_4$), and the ether was removed. Trituration of the residue with ethyl acetate gave unchanged starting material which was removed by filtration; concentration of the mother-liquor gave crystals which, recrystallised from ethyl acetate, had m. p. 159—161° (1 g.) (Found: C, 59·4; H, 5·1; N, 10·7. $C_{13}H_{14}O_2N_2S$ requires C, 59·5; H, 5·3; N, 10·7%).

Reduction of Substituted Barbituric and 2-Thiobarbituric Acids.—(i) *Reduction of 2-thiobarbituric acids with* W5 *Raney nickel.* 5-Ethyl-5-phenyl-2-thiobarbituric acid (10 g.), ethanol (250 c.c.), and freshly prepared W5 Raney nickel (Adkins and Billica, *loc. cit.*) (*ca.* 16 c.c. of alcohol-wet paste) were heated under reflux for 4 hr., then filtered through kieselguhr, and the residue was washed with hot ethanol. The solid, which separated on cooling, was crystallised from ethanol, to give *5-ethylhexahydro-4* : *6-dioxo-5-phenylpyrimidine* (primidone) (4·1 g.) m. p. 281°. The same compound was obtained when either of the three isomeric 5-chlorophenyl-5-ethyl-2-thiobarbituric acids was submitted to the same procedure.

Other hexahydro-4 : 6-dioxopyrimidines prepared by this method and by those illustrated below are shown in Table 4. When 5-phenyl-2-thiobarbituric acid was submitted to this procedure the product was 4 : 6-dihydroxy-5-phenylpyrimidine.

(ii) *Reduction of a 2-thiobarbituric acid with sodium amalgam.* 5-Ethyl-5-phenyl-2-thiobarbituric acid (10 g.), water (1·5 l.), and 3% sodium amalgam (160 g.) were stirred at room temperature for 6 hr., sufficient dilute hydrochloric acid being added, from time to time, to maintain neutrality. Next morning the procedure was repeated with more sodium amalgam (60 g.). Acidification of the supernatant liquor precipitated unchanged starting material; after removal of this, concentration of the mother-liquor yielded primidone (1 g.).

(iii) *Reduction of a 2-thiobarbituric acid with zinc and formic acid.* 5-Ethyl-5-phenyl-2-thiobarbituric acid (2 g.) in formic acid (15 c.c.) was heated on the steam-bath and zinc dust (6 g.) was added during 1 hr. and, after a further 2 hr., water (50 c.c.). The solid was collected and extracted, first with dilute aqueous sodium hydroxide to remove unchanged thiobarbituric acid, and then with hot ethanol to obtain primidone.

(iv) *Electrolytic reduction of a barbituric acid.* Phenobarbitone (5 g.), suspended in 80% w/w sulphuric acid (100 c.c.) in a porous-earthenware pot containing a U-shaped lead tube as cathode,

TABLE 4. *Hexahydro*-**4** : **6**-*dioxopyrimidines* (II).

No.	R^1	R^2	R^3	R^4	R^5	R^6	M. p.	Method of preparation	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
1	Ph	H	Me	Me	H	H	131°	(a) (i)	$C_{12}H_{14}O_2N_2$	66·2	6·4	13·0	66·1	6·4	12·9
2	Ph	Me	Me	Me	H	H	145	From No. 1	$C_{13}H_{16}O_2N_2$	67·4	6·6	11·9	67·3	6·9	12·1
3	Ph	Me	H	H	Et	H	249	(c)	$C_{13}H_{16}O_2N_2$	67·2	6·9	12·4	67·3	6·9	12·1
4	Ph	Me	H	H	Et	OMe	151 *	(e)	$C_{14}H_{18}O_3N_2$	63·8	6·6	11·2	64·1	6·9	10·7
5	Ph	Et	H	H	H	H	281	(a) (i, ii, iii, iv); (c); (d) (i)	$C_{12}H_{14}O_2N_2$	66·1	6·5	12·8	66·1	6·4	12·9
6	Ph	Et	Me	H	H	H	186	(a) (i); (d) (i)	$C_{13}H_{16}O_2N_2$	67·2	6·5	12·2	67·3	6·9	12·1
7	Ph	Et	Me	Me	H	H	106	(a) (i)	$C_{14}H_{18}O_2N_2$	68·3	7·2	11·6	68·4	7·3	11·4
8	Ph	Et	H	Et	H	H	139	(d) (i)	$C_{14}H_{18}O_2N_2$	68·3	7·5	11·7	68·4	7·3	11·4
9	Ph	Et	H	H	H	OMe	186 *	(a) (v); (d) (ii); (e)	$C_{13}H_{16}O_3N_2$	62·8	6·2	11·2	62·8	6·4	11·3
10	Ph	Et	H	H	H	OPr^i	155 *	Pr^iOH on tetrahydro-derivative	$C_{15}H_{20}O_3N_2$	64·9	7·0	10·1	65·2	7·3	10·2
11	Ph	Et	Me	H	H	OMe	157 *	(a) (v)	$C_{14}H_{18}O_3N_2$	64·6	6·7	10·8	64·2	6·9	10·7
12	Ph	Et	Me	Me	H	OMe	119	(a) (v)	$C_{16}H_{22}O_3N_2$	65·8	7·5	9·8	66·2	7·6	9·7
13	Ph	Et	H	H	Et	H	281 †	(c)	$C_{14}H_{18}O_2N_2$	68·3	7·3	11·9	68·4	7·3	11·4
14	Ph	Et	H	H	Et	H	265 ‡	(c)	"	68·5	7·5	11·3	"	"	"
15	Ph	Et	H	H	Me	OMe	160 *	(d) (ii); (e)	$C_{14}H_{18}O_3N_2$	64·3	6·8	11·0	64·1	6·9	10·7
16	Ph	Et	H	H	Et	OMe	196	(e)	$C_{15}H_{22}O_3N_2$	64·7	7·2	10·3	65·0	7·2	10·2
17	*p*-C_6H_4Cl	Et	H	H	H	H	303	(d) (i)	$C_{12}H_{13}O_2N_2Cl$	56·5	5·3	10·9	56·9	5·2	11·1
18	*m*-$NO_2{\cdot}C_6H_4$	Et	H	H	H	H	249	From No. 5	$C_{12}H_{13}O_4N_3$	55·0	5·5	15·0	54·8	5·0	15·9
19	*m*-$NH_2{\cdot}C_6H_4$	Et	H	H	H	H	300 *	From No. 18	$C_{12}H_{15}O_2N_3$	62·1	6·6	17·3	61·7	6·4	18·0
20	*m*-C_6H_4Cl	Et	H	H	H	H	280	From No. 19	$C_{12}H_{13}O_2N_2Cl$	57·3	4·8	11·3	56·9	5·2	11·1
21	*m*-$HO{\cdot}C_6H_4$	Et	H	H	H	H	295	From No. 19	$C_{12}H_{14}O_3N_2$	61·0	5·6	12·1	61·5	6·0	12·0
22	*m*-$MeO{\cdot}C_6H_4$	Et	H	H	H	H	234	From No. 21	$C_{13}H_{16}O_3N_2$	62·6	6·2	11·0	62·8	6·5	11·3
23	*m*-$NMe_2{\cdot}C_6H_4$	Et	H	H	H	H	273	From No. 19	$C_{14}H_{19}O_2N_3$	63·9	6·9	16·0	64·4	7·3	16·1
24	*m*-$NMe_3{\cdot}C_6H_4)I$	Et	H	H	H	H	160 *	From No. 23	$C_{15}H_{22}O_2N_2I$	44·6	5·5	10·4	45·1	6·1	10·2
25	*cyclo*Hexyl	Et	H	H	H	H	301	(a) (i) §	$C_{12}H_{20}O_2N_2$	64·3	4·1	12·4	64·3	4·2	12·5
26	*cyclo*Hex-1-enyl	Ph	H	H	H	H	338	(d) (i)	$C_{16}H_{14}O_2N_2$	71·7	5·3	10·5	71·7	5·3	10·5
27	Ph	Et	Ph	H	H	H	190	(a) (i)	$C_{18}H_{18}O_2N_2$	72·9	6·2	9·6	73·4	6·1	9·6

* With decomp. † α-Isomer. ‡ β-Isomer. § From 5-ethyl-5-*cyclo*hexenyl-2-thiobarbituric acid.

was electrolysed at 12 v for 2½ hr. with an initial current of 20 amp. falling to 3 amp.; the cathode compartment was contained in a beaker of 60% w/w sulphuric acid and surrounded by a cylindrical anode made of sheet-lead; water was circulated through the cathode to keep the catholyte temperature below 50°. After removal of unchanged phenobarbitone the catholyte was poured on ice, and the separated solid collected and crystallised from ethanol, to give primidone (0·1 g.).

(v) *Reduction of a 2-thiobarbituric acid with* W1 *Raney nickel or Raney cobalt.* 5-Ethyl-5-phenyl-2-thiobarbituric acid (10 g.), methanol (250 c.c.), and W1 Raney nickel (Adkins and Pavlic, *loc. cit.*) or (Raney cobalt prepared as W5 Raney nickel) (20 c.c.) were heated under reflux for 4 hr. Filtration through kieselguhr and concentration of the filtrate gave *5-ethylhexahydro-2-methoxy-4 : 6-dioxo-5-phenylpyrimidine*, m. p. 186° (decomp.) (from methanol). When ethanol was used as the solvent the corresponding 2-ethoxy-derivative was obtained; for details of this and other preparations see Table 4. When *n*- or *iso*-propanol was used as solvents the products were identical with those obtained by using W5 Raney nickel.

Reduction of 2-Alkoxy(or Alkylthio)tetrahydro-4 : 6-dioxopyrimidines.—5-Ethyltetrahydro-2-methoxy- (G.P. 249,722, Friedländer, **11**, 928) and -2-methylthio-4 : 6-dioxo-5-phenylpyrimidine were reduced to 5-ethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine when heated under reflux with either W1 or W5 Raney nickel.

Reduction of 2-Alkoxyhexahydro-4 : 6-dioxopyrimidines.—(i) 2 : 5-Diethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine. 2 : 5-Diethylhexahydro-2-methoxy-4 : 6-dioxo-5-phenylpyrimidine (13·8 g.) in glacial acetic acid (250 c.c.) was reduced by hydrogen at room temperature and pressure over Adams platinum oxide. After removal of the catalyst, the solution was evaporated to dryness and the residue fractionally crystallised from methanol, to yield the *α-form* of 2 : 5-diethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine (3·3 g.), m. p. 281°. Removal of solvent from the mother-liquor and fractional crystallisation from acetone yielded the *β-form* (2·2 g.), m. p. 265—266°, mixed m. p. with α-form 235—240°.

(ii) 5-(*p*-Chlorophenyl)-5-ethylhexahydro-4 : 6-dioxopyrimidine. This preparation exemplifies a method applicable to substances containing substituents sensitive to catalytic reduction. 5-(*p*-Chlorophenyl)-5-ethylhexahydro-2-methoxy-4 : 6-dioxopyrimidine (2 g.) and formamide (50 g.) were heated under reflux for 1 hr. The solid which separated on the addition of water was crystallised from ethanol, to give 5-p-*chlorophenyl-5-ethylhexahydro-4 : 6-dioxopyrimidine*, m. p. 303°.

Reaction of Substituted Malonodiamides with Derivatives of Formic or Acetic Acid.—(i) *With formic acid or formamide to produce hexahydro-4 : 6-dioxopyrimidine derivatives.* *C*-Ethyl-*C*-phenylmalonodiamide monohydrate (22·4 g.) and 98% formic acid (6 c.c.) were heated to 190° (internal temp.) for 1 hr.; formic acid (8 × 4 c.c.) was then added during 2 hr. and heating was continued for a further 2 hr. After cooling, the mixture was triturated with methanol, and the solid collected and washed with methanol, to give 5-ethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine (9 g.). The same product was obtained when *N*-formyl- or *NN'*-bishydroxymethylmalonodiamide was heated with formic acid in boiling dimethylformamide.

The following method is to be preferred with *N*-monoalkylmalonodiamides: *CN*-diethyl-*C*-phenylmalonodiamide (10 g.) and formamide (80 c.c.) were heated under vigorous reflux for 3 hr. The solid which separated on cooling and dilution with water crystallised from aqueous ethanol, to give 1 : 5-*diethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine*, m. p. 138—139°.

(ii) *With ethyl formate or ethyl acetate to produce 2-alkoxyhexahydro-4 : 6-dioxopyrimidine.* *C*-Ethyl-*C*-phenylmalonodiamide hydrate (112 g.) was dried by distillation with toluene and filtered. The toluene-wet filter-cake was then added, together with ethyl acetate (50 g.), to a solution of sodium (11·5 g.) in methanol (200 c.c.). After 4 hours' heating under reflux the mixture was cooled, neutralised with methanolic hydrogen chloride, and filtered. The residue, after being washed with water, crystallised from methanol, to give *5-ethylhexahydro-2-methoxy-2-methyl-4 : 6-dioxo-5-phenylpyrimidine* (35 g.), m. p. 160° (decomp.).

A similar procedure may be employed with ethyl formate, to give 2-alkoxyhexahydro-4 : 6-dioxopyrimidines without further 2-substituents. *C*-Ethyl-*N*-methyl-*C*-phenylmalonodiamide with ethyl formate gave a small amount of *di-(α-methylcarbamoyl-α-phenylbutyryl)formamidine*, m. p. 193—194° (from aqueous methanol) (Found: C, 66·8; H, 6·5; N, 12·8. $C_{25}H_{30}O_4N_4$ requires C, 66·7; H, 6·7; N, 12·4%), together with much unchanged starting material.

Reaction of *C*-ethyl-*N*-formyl-*C*-phenylmalondiamide with sodium methoxide under similar conditions yielded 5-ethylhexahydro-2-methoxy-4 : 6-dioxo-5-phenylpyrimidine.

Reaction of Substituted Diethyl Malonates with Amidines.—To a solution of sodium (9·2 g.) in methanol (200 c.c.), propionamidine hydrochloride (21·7 g.) and ethyl methylphenyl-

malonate (50 g.) were added. After being heated at 105—110° for 20 hr., the mixture was cooled and neutralised with methanolic hydrogen chloride. After filtration, the solid was washed first with methanol, then with water, and crystallised from methanol, to give *2-ethyl-hexahydro-2-methoxy-5-methyl-4 : 6-dioxo-5-phenylpyrimidine* (24·0 g.), m. p. 151—152°, when acetamidine or formamidine was employed the yields were much reduced. In addition, in the case of formamidine, it was necessary to continue the reaction for 5 days and at a low temperature, 0° initially.

5-Ethylhexahydro-5-m-nitrophenyl-4 : 6-dioxopyrimidine.—To 5-ethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine (50 g.) in 98% sulphuric acid (200 c.c.), a mixture of nitric acid (*d* 1·5; 11 c.c.) and 98% sulphuric acid (50 c.c.) was added, with stirring, at <3°. Then the mixture was poured on ice (600 g.), and the solid which separated was washed with cold water and crystallised from 80% aqueous ethanol, to give the *nitro*-compound (36 g.), m. p. 248—249°. This substance (22 g.) in acetic acid (44 c.c.) was reduced with hydrogen over Adams platinum catalyst at 48 atm. and room temperature during 30 min. After removal of the catalyst the solution was evaporated to dryness, and the residue was stirred with excess of cold 2N-hydrochloric acid and filtered. The solid *azoxy*-compound, m. p. >350°, was digested with boiling ethanol for analysis (Found : C, 60·9; H, 5·7; N, 16·8. $C_{24}H_{26}O_5N_6$ requires C, 60·2; H, 5·4; N, 17·6%). Basification of the filtrate gave the *amino*-compound, m. p. 299—300° (decomp.) (from aqueous ethanol). This was converted by standard procedures into the corresponding m-*chloro*- (identical with material synthesised from *m*-chlorotoluene), m-*hydroxy*-, m-*dimethylamino*-derivative, and the m-*trimethylammonium iodide* (see Table 4). The *m*-hydroxy-compound was converted into the m-*methoxy*-derivative by methyl sulphate in aqueous sodium hydroxide.

Hexahydro-1 : 3 : 5-trimethyl-4 : 6-dioxo-5-phenylpyrimidine.—To a solution of hexahydro-1 : 3-dimethyl-4 : 6-dioxo-5-phenylpyrimidine (2·18 g.) and sodium hydroxide (0·6 g.) in water (10 c.c.), methyl sulphate (1·6 c.c.) was added with vigorous stirring. When the solution became acid further portions of sodium hydroxide (0·3 g.) and methyl sulphate (0·8 c.c.) were added. The product which separated after the addition of excess of alkali was filtered off and crystallised from water, to give *hexahydro-1 : 3 : 5-trimethyl-4 : 6-dioxo-5-phenylpyrimidine*, m. p. 144—145°.

1 : 5-Diethyltetrahydro-2-methyl-4 : 6-dioxo-5-phenylpyrimidine.—*CN*-Diethyl-*C*-phenylmalonodiamide (4·7 g.), acetyl chloride (9·6 g.), and glacial acetic acid (1·2 c.c.) were heated at 100° in a sealed vessel for 1 hr. After cooling, the *hydrochloride* was collected, washed with acetyl chloride, then with ether, and crystallised from glacial acetic acid; it had m. p. 211° (decomp.) (Found : C, 61·3; H, 6·2; N, 9·7; Cl, 12·3. $C_{15}H_{19}O_2N_2Cl$ requires C, 61·0; H, 6·1; N, 9·5; Cl, 12·1%).

In addition to *tetrahydro-2-methyl-4 : 6-dioxo-5-phenyl-5-n-propylpyrimidine hydrochloride*, m. p. 215° (decomp.) (Found : C, 59·5; H, 6·1; N, 10·2; Cl, 12·5. $C_{14}H_{16}O_2N_2$,HCl requires C, 59·7; H, 6·1; N, 10·0; Cl, 12·6%), *C*-phenyl-*C*-*n*-propylmalonodiamide with acetyl chloride under similar conditions yielded *NN'-diacetyl-C-phenyl-C-n-propylmalonodiamide*, m. p. 155—156° (from aqueous methanol) (Found : C, 62·8; H, 6·5; N, 8·8. $C_{16}H_{20}O_4N_2$ requires C, 63·0; H, 6·6; N, 9·2%). Reaction of *C*-ethyl-*C*-phenylmalonodiamide with keten in xylene solution at 100—120° gave, on removal of the solvent, a gum which, on trituration with light petroleum and crystallisation from aqueous methanol, gave *N-acetyl-α-cyano-α-phenylbutyramide*, m. p. 101° (Found : C, 67·7; H, 6·0; N, 12·5. $C_{13}H_{14}O_2N_2$ requires C, 67·9; H, 6·1; N, 12·2%), together with ethylphenylmalononitrile.

5-m-Chlorophenyl-5-ethylbarbituric Acid.—To *C-m*-chlorophenyl-*C*-ethylmalonodiamide (12 g.), dissolved in a solution of sodium (7 g.) in methanol (150 c.c.), diethyl carbonate (5·2 g.) was added and the whole was heated under reflux for 1·5 hr. At the end of this time and again after a similar period, two further lots of diethyl carbonate (5·2 g.) were added. After a final period of 1·5 hr., the mixture was cooled, diluted with water (200 c.c.), and filtered (charcoal). The solid which separated on acidification of the filtrate with dilute hydrochloric acid was collected and crystallised from methanol, to give *5-m-chlorophenyl-5-ethylbarbituric acid* (7 g.), m. p. 244°, undepressed on admixture with the acid prepared by Bourquet and Adams's method (*loc. cit.*) (Found : C, 53·7; H, 4·1; N, 9·5. $C_{12}H_{11}O_3N_2Cl$ requires C, 54·0; H, 4·1; N, 10·0%).

5-Ethyltetrahydro-4 : 6-dioxo-5-phenylpyrimidine.—5-Ethyl-2-methoxy-4 : 6-dioxo-5-phenylhexahydropyrimidine (10 g.) in ether (100 c.c.) was saturated with hydrogen chloride, with ice-cooling. After 2 hr. the *hydrochloride* was collected and, crystallised from glacial acetic acid, had m. p. 370° (Found : C, 55·6; H, 5·1; N, 11·2; Cl, 13·6. $C_{12}H_{12}O_2N_2$,HCl requires C, 55·4;

H, 5·1; N, 11·1; C, 14·0%). A solution of the hydrochloride (8 g.) in water (20 c.c.) was adjusted to pH 6—7 by the addition of saturated potassium acetate solution; after 3 hr. the crystalline *hydrate* was collected; recrystallised from water (below 60°), it had m. p. 122—123° (decomp.) (Found: C, 61·4; H, 6·0; N, 11·9. $C_{12}H_{12}O_2N_2,H_2O$ requires C, 61·5; H, 6·0; N, 12·0%). Boiling the hydrate with water for 5 min. gave NN-*di*-(α-*carbamoyl*-α-*phenylbutyryl*)-*formamidine*, m. p. 205° (decomp.) (from methanol) (Found: C, 64·5; H, 5·8; N, 13·1. $C_{23}H_{26}O_4N_4$ requires C, 65·4; H, 6·2; N, 13·3%); longer boiling gave *C*-ethyl-*C*-phenylmalonodiamide. Heating the hydrate at 120°/0·01 mm. or 2-alkoxy-5-ethylhexahydro-5-phenylpyrimidine-4 : 6-dione at 180—185°/0·01 mm. for 2 hr. gave crude 5-ethyltetrahydro-4 : 6-dioxo-5-phenylpyrimidine, m. p. 116° (decomp.) (Found: C, 62·8; H, 6·0; N, 12·5. Calc. for $C_{12}H_{12}O_2N_2$: C, 66·7; H, 5·6; N, 12·9%), which could not be purified. Further heating at 200° yielded an amorphous polymer insoluble in all solvents. The base, hydrate, and hydrochloride reacted with a wide range of alcohols to give the corresponding 2-alkoxy-derivative, *e.g.*, with *iso*propyl alcohol to give 5-*ethylhexahydro*-4 : 6-*dioxo*-5-*phenyl*-2-iso*propoxypyrimidine*, m. p. 155—156° (decomp.).

5-Ethylhexahydro-2-methoxy-4 : 6-dioxo-5-phenylpyrimidine (2·5 g.), 37% formaldehyde (8 c.c.), potassium carbonate (0·1 g.), and water (20 c.c.) were warmed to 40° to complete dissolution; on cooling, 5-*ethylhexahydro*-1 : 3-*bishydroxymethyl*-2-*methoxy*-4 : 6-*dioxo*-5-*phenylpyrimidine* separated, having m. p. 127—128° (decomp. at 132°) (Found: C, 57·8; H, 6·3; N, 9·1. $C_{15}H_{20}O_5N_2$ requires C, 58·4; H, 6·5; N, 9·1%). This substance could not be crystallised without decomposition.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, DYESTUFFS DIVISION, HEXAGON HOUSE, BLACKLEY, MANCHESTER, 9. [*Received, April 15th*, 1954.]

The Oxidation of Alkyl Sulphides.

By D. EDWARDS and J. B. STENLAKE.

[Reprint Order No. 5344.]

Oxidation of saturated alkyl sulphides with chromic acid in pyridine and with manganese dioxide in light petroleum afforded the corresponding sulphoxides. Allyl sulphoxide has also been obtained by oxidation of allyl sulphide with manganese dioxide in light petroleum.

OXIDATION of sulphides to sulphoxides and sulphones can be brought about by many reagents, including 30% hydrogen peroxide in acetic acid (Gazdar and Smiles, *J.*, 1908, **93**, 1834), nitric acid or potassium permanganate (Beckmann, *J. pr. Chem.*, 1878, **17**, 441), chromic acid (Knoll, *ibid.*, 1926, **113**, 40), and perbenzoic acid (Lewin, *ibid.*, 1928, **118**, 282). The state of oxidation achieved depends largely on reaction conditions, though mixtures of sulphoxides and sulphones are often obtained (Berg, *J.*, 1949, 1991). Chromic acid in acetic acid, alone, appears to be specific for oxidation to the sulphoxide (Knoll, *loc. cit.*). Yields are poor in the direct oxidation of unsaturated sulphides with these mentioned reagents (Price and Gillis, *J. Amer. Chem. Soc.*, 1953, **75**, 4750), presumably owing to concurrent oxidation at the centre of unsaturation. Indirect methods, involving dehydrohalogenation of β-halogeno-sulphones, offer a more satisfactory route to αβ-unsaturated sulphones, the intermediate halogeno-sulphones being readily available in good yield by oxidation of the corresponding sulphides (Price and Morita, *ibid.*, p. 4747).

The successful oxidation of unsaturated alcohols by chromic acid in pyridine (Poos, Arth, Beyler, and Sarett, *ibid.*, p. 422), and manganese dioxide in light petroleum (Ball, Goodwin, and Morton, *Biochem. J.*, 1948, **42**, 516; Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094) prompted investigation of their use with unsaturated aliphatic sulphides. Preliminary experiments were conducted with saturated aliphatic sulphides. In no case studied did oxidation proceed beyond the sulphoxide.

Under Poos, Arth, Beyler, and Sarett's conditions (*loc. cit.*), di-*n*-butyl sulphide and chromic acid in pyridine at room temperature gave di-*n*-butyl sulphoxide in 49% yield without trace of the sulphone. Use of a large excess of reagent both at room temperature

and at 100° also gave only the sulphoxide. Di-*n*-butyl sulphoxide so obtained was characterised by its known physical constants and by conversion into toluene-*p*-sulphonyl-di-*n*-butylsulphilimine $Bu^n_2S{:}N{\cdot}SO_2{\cdot}C_6H_4Me$-*p* by condensation with toluene-*p*-sulphonamide by use of phosphoric oxide in chloroform (cf. Tarbell and Weaver, *J. Amer. Chem. Soc.*, 1941, **63**, 2939). The product was identical (m. p. and mixed m. p.) with that obtained from the sulphide and chloramine-T (cf. Mann and Pope, *J.*, 1922, 1052).

Similar oxidation of dibenzyl sulphide gave dibenzyl sulphoxide in 70% yield after 5 days at room temperature.

Similar oxidations of diallyl sulphide proved abortive. Products containing sulphur were isolated in only minute amounts, insufficient for identification. Although in all experiments difficulties were encountered with emulsions, our failure to isolate either product or starting material could not be attributed to this cause, but much allyl sulphide was lost through co-distillation with the extraction solvents. These difficulties were largely overcome by the use of manganese dioxide in light petroleum.

Oxidation of di-*n*-butyl sulphide with activated manganese dioxide in light petroleum gave the sulphoxide exclusively; reaction was slow at room temperature, but a yield of 71% was obtained after 85 hr. Dibenzyl sulphoxide was obtained, similarly, in 74% yield after 72 hr. at room temperature. Little, if any, acceleration was observed at higher temperatures. The method is suitable for oxidation of diallyl sulphide which, after 76 hr., gave diallyl sulphoxide in 13% yield. Longer reaction times (7 days) and higher temperatures failed to improve the yield. The only aromatic sulphide examined, 2 : 2′ : 4 : 4′-tetranitrodiphenyl sulphide, was not oxidised by manganese dioxide, but was recovered quantitatively.

Experimental

Oxidations with Chromic Acid in Pyridine.—(a) *Di-*n*-butyl sulphoxide.* Chromic acid (18·5 g.) was added during 1 hr., with stirring, to di-*n*-butyl sulphide (5·5 g.) in pyridine (180 ml.). Next morning the mixture was poured into water (1 l.) and extracted with ether, and the extract dried (Na_2SO_4) and evaporated. Distillation gave di-*n*-butyl sulphoxide (3 g., 49%) as a colourless liquid, which crystallised only under anhydrous conditions m. p. 31—32° (lit., m. p. 32°).

On exposure to air the crystals rapidly absorb moisture and liquefy, a process which is reversed on dehydration.

(b) *Dibenzyl sulphoxide.* Chromic acid (6·2 g.) was added during 1 hr. with stirring to dibenzyl sulphide (1·25 g.) in pyridine (60 ml.). After 5 days the mixture was poured into water (500 ml.) and extracted with benzene, and the extract dried (Na_2SO_4) and evaporated, to give dibenzyl sulphoxide (0·95 g., 71%), m. p. 133—134° (from light petroleum). Bohme (*Ber.*, 1937, **70**, 383) gives m. p. 134—135°.

Oxidations with Manganese Dioxide in Light Petroleum.—Manganese dioxide was prepared by precipitation from manganese sulphate and potassium permanganate as described by Ball, Goodwin, and Morton (*loc. cit.*). Light petroleum (b. p. 40—60°) was sodium-dried.

(a) *Di-*n*-butyl sulphoxide.* Di-*n*-butyl sulphide (1·2 g.) in light petroleum (120 ml.) was shaken continuously with manganese dioxide (12·7 g.) for 85 hr. Filtration and evaporation gave a small quantity of di-*n*-butyl sulphoxide. The bulk of product was isolated by continuous extraction of the manganese dioxide with benzene, which after evaporation and distillation gave di-*n*-butyl sulphoxide (0·97 g., 71%) as an oil, crystallising under anhydrous conditions (m. p. 31—32°).

(b) *Dibenzyl sulphoxide.* Dibenzyl sulphide (0·74 g.) in light petroleum (75 ml.) was shaken continuously with manganese dioxide (7·5 g.) for 72 hr. Filtration and evaporation gave only traces of unchanged sulphide. The product was isolated by continuous extraction of the manganese dioxide with chloroform, which on evaporation gave dibenzyl sulphoxide (0·5 g., 74%), m. p. 133—134° (from light petroleum).

(c) *Diallyl sulphoxide.* Diallyl sulphide (2·5 g.) in light petroleum (70 ml.) was shaken continuously with manganese dioxide (37·5 g.) for 76 hr. Filtration and evaporation gave a small quantity of unchanged sulphide. The product, isolated as in (*b*), was a brownish-red liquid (1·28 g., 45%), which on distillation yielded diallyl sulphoxide (0·36 g., 13%), b. p. 100—110° (bath)/3 mm., $n_D^{17\cdot5}$ 1·5117, $d_{17\cdot5}^{17\cdot5}$ 1·034. Lewin (*loc. cit.*) gives n_D^{20} 1·5115, d_4^{20} 1·0261.

*Toluene-*p*-sulphonyldi-*n*-butylsulphilimine.*—(a) *From di-*n*-butyl sulphide.* Di-*n*-butyl

sulphide (0·68 g.) was shaken vigorously with cold saturated aqueous chloramine-T (1·36 g.). The solid which rapidly separated was filtered off after 1 hr. and recrystallised from benzene–light petroleum, to yield the *sulphilimine* in colourless needles, m. p. 77·5—78° (Found: S, 19·5. $C_{15}H_{25}O_3NS$ requires S, 20·3%).

(b) *From di-*n*-butyl sulphoxide.* Di-*n*-butyl sulphoxide (0·55 g.) and toluene-*p*-sulphonamide (0·56 g.) were refluxed with phosphoric oxide (0·35 g.) in chloroform (4 ml.) for 30 min. Phosphoric oxide (0·35 g.) was then added and refluxing continued for a further 30 min. The solution was decanted from the sludge whilst still hot, cooled, and washed with sodium hydroxide solution (10%). Evaporation of the chloroform gave the sulphilimine in colourless needles, m. p. 77·5—78° (from benzene–light petroleum), alone or mixed with a specimen prepared as described under (a).

THE SCHOOL OF PHARMACY,
THE ROYAL TECHNICAL COLLEGE, GLASGOW.

[*Received, April 30th*, 1954.]

The Degradation of Carbohydrates by Alkali. Part VI. Laminaribiose and Turanose.*

By W. M. CORBETT and J. KENNER.

[Reprint Order No. 5365.]

The observed approximate agreement in the rates of degradation of laminaribiose and of turanose by lime-water to glucometasaccharinic acid and glucose is attributed to their having a common doubly charged enediol ion. Earlier formulations, in this series, of similar reactions are correspondingly revised and a general interpretation of the behaviour of glucose towards varying strengths of alkali is provided.

IT is implicit in the β-alkoxycarbonyl mechanism of the alkaline degradation of disaccharides and of alkylated monoses that such degradation should be especially easy when the glycoside or alkyl group is attached in the β-position to the carbonyl group of the monose. Details are now communicated in regard to laminaribiose (3-*O*-β-D-glucopyranosyl-D-glucopyranose), the first case in which this inference was confirmed (Corbett, Kenner, and Richards, *Chem. and Ind.*, 1953, 154). As was further expected, the products of its treatment with lime-water proved to be essentially a mixture of the α- and the β-form of metasaccharinic acid (II) with glucose and fructose. Graphs of the respective courses of biose decomposition, monose formation, and acid formation are closely concordant until, in the later stages of the reaction, some degradation of monose asserts itself.

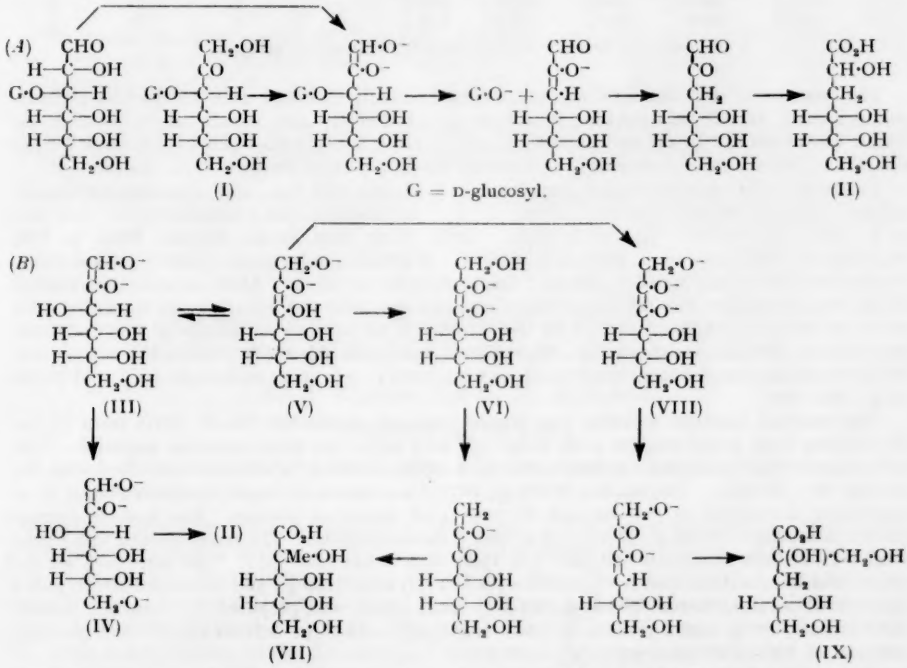
Turanose is the ketose, 3-*O*-α-D-glucopyranosyl-D-fructose (cf. I) (Isbell, *J. Res. Nat. Bur. Stand.*, 1941, **26**, 35), and Isbell interpreted the results of his study of its behaviour towards N-potassium hydroxide in terms of hydrolysis to equimolecular proportions of fructose and glucose, citing, as evidence of formation of monosaccharide, the isolation of potassium arabonate after oxidation of the resulting alkaline solution. However, our experiments with lime-water demonstrated the formation, as in the case of laminaribiose, of glucometasaccharinic acid as the other main product. Some lactic acid was also formed, as it was from 3-*O*-methylfructose (Kenner and Richards, *J.*, 1954, 278).

The degradation of reducing sugars by anion-exchange resins, observed by Rebenfeld and Pacsu (*J. Amer. Chem. Soc.*, 1953, **75**, 4370; cf. Hulme, *Nature*, 1953, **171**, 610) occurs by a mechanism analogous to that for lime-water, and their observation that the degradation of turanose by the carbonate form of Amberlite IRA-400 resin liberates only glucose (and no fructose) is in agreement with our results. With more basic reagents (*e.g.*, calcium hydroxide or the hydroxide form of IRA-400) fructose is produced at a later stage by a Lobry de Bruyn–van Ekenstein transformation of glucose (*Rec. Trav. chim.*, 1895, **14**, 203; 1897, **16**, 251, 274, 278).

A further and very significant relation between the results obtained with the 3-*O*-

* Part V, *J.*, 1954, 1789.

methyl- and the 3-*O*-glucosyl-hexoses lay in the approximately equal rates of degradation of aldose and ketose in each case. It thus appears that a common anion is concerned and compliance with this is secured by postulating charges on both the 1- and the 2-oxygen atom of the common enediol form. First and second dissociation constants of glucose and fructose have been recorded by various workers (Hirsch and Schlago, *Z. physikal. Chem.*, 1929, **41**, 387; Stearn, *J. Phys. Chem.*, 1931, **35**, 2226; Shaffer and Harned, *J. Biol. Chem.*, 1931, **93**, 311; Urban and Shaffer, *ibid.*, 1932, **94**, 697; Urban and Williams, *ibid.*, 1933, **100**, 237) and a third constant asserts itself at pH 13·6 (Urban and Williams, *loc. cit.*). Although calculation on this basis indicates that under our experimental conditions only about 4% of glucose would be present in the doubly charged form as against 70% in the singly charged form, it is nevertheless evident that the former is much more prone to extrude an anion and so, when it is available, is the rate-determining organic reactant. We thus have the annexed reactions (*A*), with corresponding amendment of reaction schemes in earlier papers of this series. In particular, the scheme (*B*) expresses the behaviour of glucose and fructose towards dilute and concentrated alkali respectively, though there can obviously be no sharp line of distinction between the two. Since a primary is more acidic than an isomeric secondary alcohol, the anion (III), common to glucose and fructose, may be expected in concentrated alkali to furnish (IV) from which meta-



saccharinic acid will be derived; on the other hand, the anion (III) is convertible by prototropy into (V) which leads, in relatively weak alkali, through (VI) to saccharinic acid (VII) but in concentrated alkali through (VIII) to *iso*saccharinic acid (IX). Nef obtained meta- with a small proportion of *iso*-saccharinic acid from glucose by the action of 8N-sodium hydroxide (*Annalen*, 1910, **376**, 89).

Experimental

Laminaribiose.—The Table records observations made when a solution of laminaribiose (Bächli and Percival, *J.*, 1952, 1243) {0·2869 g.; m. p. 182—186°; $[\alpha]_D^{21}$ +18·1° (*c*, 3·21 in H_2O)} in oxygen-free lime-water (50 ml.; 0·0383N) was kept at 25°. The course of the reaction

was followed by determining at intervals (*a*) biose and monose (cf. Corbett, *Chem. and Ind.*, 1953, 1285), (*b*) saccharinic acid (Bamford, Bamford, and Collins, *Proc. Roy. Soc.*, 1950, *A*, **204**, 85), and (*c*) total acidity (by direct titration). The general agreement of the experimental results in regard to (*a*) and (*b*) demonstrates the general accuracy of these determinations but the earlier results under (*c*) in relation to low concentrations are manifestly unsatisfactory.

Degradation of laminaribiose by saturated lime-water at 25°.

Time (hr.)	α_D	Monoses formed (%)	Laminaribiose decompd. (%)	Saccharinic acids formed (%)	Total acids formed (%)	Paper chromatography *			
						Laminaribiose	Glucose	Fructose	Sacc. acids
0·1	+0·03°	7·0	4·3	7·7	3·3	3	1	—	—
0·5	0·03	19·8	17·6	11·6	11·9	3	1	—	1
1	0·04	31·5	29·4	31·1	21·5	3	1	—	1
2	0·05	54·3	51·1	49·0	42·7	2	2	1	1
3	0·04	65·8	64·4	62·3	55·3	2	2	1	1
4	0·03	74·6	74·7	71·6	65·7	1	2	1	1
5	0·02	75·7	77·0	73·9	72·3	1	2	1	1
6	±0·00	81·5	81·3	79·8	77·1	1	2	1	1
12	±0·00	88·4	87·7	84·2	92·2	1	2	2	2
24	−0·02	86·6	92·1	99·2	104·5	—	2	2	2
27	−0·02	86·0	93·5	102·9	118·5	—	2	2	2
48	−0·04	84·0	100·0	114·4	125·8	—	2	1	2

* Numerals denote relative intensity, 3 being the greatest.

The saccharinic acid obtained was chromatographically identical with the metasaccharinic acid prepared, as will be described in a later paper, directly and as sole acidic product, by similar treatment of "insoluble" laminarin, and thus available in the quantity adequate for the separation into α- and β-isomerides requisite for its proper characterisation (cf. Nef, *loc. cit.*).

Turanose.—The material used, supplied by L. Light and Co., was chromatographically uniform towards butanol–pyridine–water (3 : 2 : 1·5) (alkaline silver nitrate spray) and had m. p. 168°, $[\alpha]_D^{21}$ +74·7° (*c*, 2·60 in H_2O). Bates (Nat. Bur. Stand. Circular **6440**, p. 758, Washington 1942) gives m. p. 157°, $[\alpha]_D^{20}$ +75·8°. A solution of turanose (1·230 g.) in saturated oxygen-free lime-water (0·043N) (250 ml.) was kept at 25° for 48 hr. After quantitative removal of calcium as oxalate, the filtered solution was concentrated and exhaustively extracted with ether, the extract being kept neutral by the presence of an aqueous suspension of zinc carbonate (see Nadeau, Newlin, and Evans, *J. Amer. Chem. Soc.*, 1933, **55**, 4957). From the extract was obtained zinc lactate (0·231 g.) from which was prepared (−)-brucine DL-lactate, m. p. and mixed m. p. 190—200°.

The residual aqueous solution was passed through Amberlite IR-4B (OH) resin (5 g.), the column then being washed with water (25 ml.) until free from reducing material. Concentration of the eluate and washings afforded a syrup (0·839 g.) which was extracted with dry acetone (3 × 20 ml.). The residue (0·693 g., 107%) was shown by paper chromatography to be essentially a mixture of glucose and fructose with traces of psicose. The acetone extract yielded a mixture (0·136 g., 23·4%) of α- and β-metasaccharin. The resin column was eluted with 0·1M-sodium carbonate (50 ml.) and then with water (100 ml.). The combined eluates were freed from sodium ions by Amberlite IR-120 (H) resin (100 g.) and concentrated, to give a mixture of metasaccharins (0·130 g., 22·3%) from which was prepared (−)-brucine β-metasaccharinate, m. p. and mixed m. p. 145—168°, $[\alpha]_D^{22}$ −38·0° (*c*, 0·21 in H_2O). Nef (*loc. cit.*) gives m. p. 130—150° (decomp.), $[\alpha]_D$ −33·1°.

Tests preliminary to a kinetic study of the above reaction showed the charcoal–Celite column techniques used in previous instances to be inadequate in this case owing to elution of some turanose with the monosaccharides. Another method, based on reducing power determined by the Hagedorn–Jensen procedure was therefore evolved [though it was subsequently found possible to separate glucose and turanose by using charcoal–Celite columns of increased length (Corbett, *loc. cit.*)]. In this way 0·342 mg. of turanose and 0·360 mg. of glucose were found to be equivalent to 1·98 and 4·72 ml. respectively of 0·002N-thiosulphate. Hydrolysis of an aqueous solution (2 ml.) of the ketose (0·012 g.) in N-sulphuric acid (5 ml.) having been shown to be complete after 3 hr. at 100°, the procedure was applied to mixtures of glucose and turanose equivalent to x and y ml. of thiosulphate solution respectively. Hence before hydrolysis, titre $A = (x + y)$ ml., and after hydrolysis $B = (x + 2{\cdot}38y)$ ml., whence $B - A = 1{\cdot}38y$ ml.

Then a solution (50 ml.) of turanose (0·2845 g.) in saturated oxygen-free lime-water (0·0333N) was kept at 25°; at noted periods aliquot portions (2 ml.) were withdrawn and run into 0·01N-sulphuric acid (10 ml.); after ½ hr. the solution was back-titrated with 0·01N-sodium hydroxide to the first semi-permanent end-point of phenolphthalein. The solution was diluted to 50 ml., the rotation observed, and the total reducing power before and after acid hydrolysis estimated on samples of 2 ml. The tabulated data were thus obtained.

Degradation of turanose by saturated lime-water at 25°.

Time (hr.)	α_D	Turanose decompd. (%)	Monoses formed (%)	Total acids formed (%)	Paper chromatography *			
					Turanose	Glucose	Fructose	Sacc. acids
0·1	+0·06°	15·0	14·2	3·0	3	1	—	—
1	0·04	32·7	28·4	39·4	3	1	—	1
2	0·01	48·3	41·7	64·8	2	2	—	1
3	±0·00	52·5	50·0	74·4	1	2	—	2
4	±0·00	61·9	59·2	79·5	1	2	1	2
5	±0·00	75·1	65·8	87·0	1	2	1	2
6	±0·00	80·1	76·6	93·0	—	2	1	2
7	±0·00	89·1	84·3	96·8	—	2	1	2
24	±0·00	90·0	86·7	106·0	—	2	2	2
31	±0·00	94·0	85·0	112·5	—	2	2	2
48	±0·00	98·6	78·4	131·8	—	2	2	2

* Numerals denote relative intensity, 3 being the greatest.

We thank the Director of the Institute of Seaweed Research for supplies of laminarin. This work and that in the following two papers forms part of the programme of fundamental research undertaken by the Council of the British Rayon Research Association.

This work, and that in the two following papers, forms part of the programme of fundamental research undertaken by the Council of the British Rayon Research Association.

THE BRITISH RAYON RESEARCH ASSOCIATION, HEALD GREEN LABORATORIES,
WYTHENSHAWE, MANCHESTER. [*Received, May 5th*, 1954.]

---

*The Degradation of Carbohydrates by Alkali. Part VII.** 5-O-*Benzyl-* *and* 3 : 5-O-*Benzylidene-2-deoxy-*D-*ribose.*

By J. KENNER and G. N. RICHARDS.

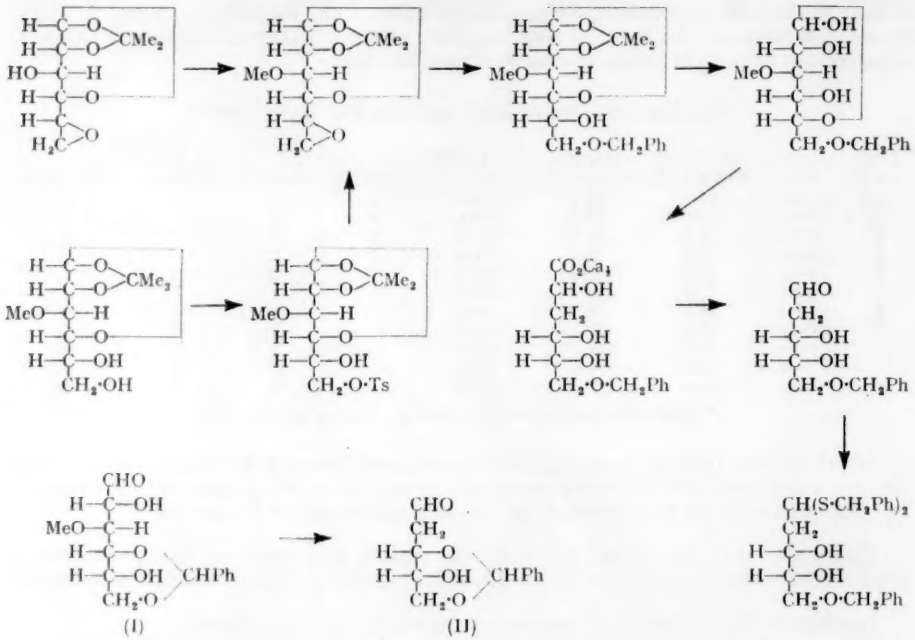
[Reprint Order No. 5366.]

Preparation of 5-*O*-benzyl- and of 3 : 5-*O*-benzylidene-2-deoxy-D-ribose is described.

THE generalisation in Parts III and IV of this series (Kenner and Richards, *J.*, 1954, 278, 1784) indicates that a desired derivative of either a meta- or an *iso*-glucosaccharinic acid will be accessible, uncontaminated by isomerides, from the corresponding derivative of respectively a 3- or a 4-*O*-alkylglucose. Furthermore, although 2-deoxy-D-ribose is now easily accessible (Richards, *J.*, 1954, this issue) some of its 5-*O*-derivatives are desirable for use in incorporation of the 2-deoxy-D-ribofuranosyl grouping into molecular structures, *e.g.*, deoxynucleosides (cf. G. W. Kenner, Taylor, and Todd, *J.*, 1949, 1620). Accordingly we have applied our principles to the preparation of 5-*O*-benzyl-2-deoxy-D-ribose from 3-*O*-methyl-6-*O*-benzyl-D-glucose through the corresponding 6-*O*-benzyl-D-glucometa-saccharinic acid. The annexed scheme exhibits the alternative series of reactions involved, starting from the 6-*O*-toluene-*p*-sulphonyl derivative of either 1 : 2-*O*-*iso*propylidene-D-glucose or its 3-*O*-methyl derivative. Similarly the 4 : 6-*O*-benzylidene derivative of 3-*O*-methyl-D-glucose (I) has been converted into 3 : 5-*O*-benzylidene-2-deoxy-D-ribose (II). In this case it was possible to correlate one of the intermediate 4 : 6-*O*-benzylidenemeta-

* Part VI, preceding paper.

saccharinic acids with authentic 3-deoxy-γ-D-mannonolactone, and also to convert the benzylideneribose derivative into 2-deoxy-D-ribose itself.



Experimental

6-O-*Benzyl*-3-O-*methyl*-D-*glucose*.—(a) **5 : 6-*Anhydro*-3-O-*methyl*-1 : 2-O-iso*propylidene*-α-D-*glucose*.** 5 : 6-Anhydro-1 : 2-*O*-*iso*propylidene-α-D-glucose (30·0 g.) (Ohle and Vargha, *Ber.*, 1929, **62**, 2435) was methylated thrice with silver oxide and methyl iodide, and the resulting 3-O-*methyl ether* distilled at 98°/0·3 mm. The distillate (29·54 g., 92%) showed n_D^{17} 1·4586, $[\alpha]_D^{21}$ −69·6° (*c*, 2·5 in $CHCl_3$) (Found: C, 55·5; H, 7·6. $C_{10}H_{16}O_5$ requires C, 55·5; H, 7·5%).

6-O-*Benzyl*-3-O-*methyl*-1 : 2-O-iso*propylidene*-α-D-*glucose*. The above anhydro-sugar (18·64 g.) and sodium benzyloxide (from 10 g. of sodium) in oxygen-free benzyl alcohol (150 ml.) were kept for 2 days at 35°. After acidification with 20% acetic acid (250 ml.) the mixture was extracted with ether, and the extracts were washed with aqueous sodium hydrogen carbonate and with water and then evaporated under reduced pressure. After removal of benzyl alcohol at 0·1 mm., the residual syrupy *product* distilled at 185—190° (bath-temp.)/0·1 mm. It showed n_D^{19} 1·5062, $[\alpha]_D^{21}$ −37° (*c*, 2 in $CHCl_3$) (Found: C, 62·7; H, 7·4. $C_{17}H_{24}O_6$ requires C, 62·9; H, 7·5%).

(b) A solution of 3-*O*-methyl-1 : 2-5 : 6-di-*O*-*iso*propylidene-α-D-glucose (9·96 g.; Glen, Myers, and Grant, *J.*, 1951, 2568) in a mixture of acetic acid (400 ml.) and water (100 ml.) was kept at 20° ± 1° for 48 hr. and then concentrated to a syrup at 40° under reduced pressure. The residual syrup was diluted with ethanol (100 ml.), neutralised with barium carbonate, and further diluted with ether (100 ml.). After removal of solvent from the filtered solution, 3-*O*-methyl-1 : 2-*O*-*iso*propylidene-α-D-glucose (6·4 g., 75%) distilled at 170—180° (bath-temp.)/0·1 mm. and had n_D^{17} 1·4720, $[\alpha]_D^{20}$ −36·8° (*c*, 4 in EtOH) (Found: C, 51·4; H, 7·5. Calc. for $C_{10}H_{18}O_6$: C, 51·3; H, 7·7%) [Freudenberg, Dürr, and Hochstetter (*Ber.*, 1928, **61**, 1735) reported b. p. 173—175°/1 mm.]. A solution of this product (9·98 g.) in dry pyridine (50 ml.) was treated with toluene-*p*-sulphonyl chloride (8·9 g.) at room temperature for 24 hr. and subsequently poured into ice-water. The product was extracted with chloroform and treated in the usual way, to yield crude 3-*O*-methyl-1 : 2-*O*-*iso*propylidene-6-*O*-toluene-*p*-sulphonyl-α-D-glucose as a pale yellow syrup. This was dried (P_2O_5 at 50°/0·1 mm.) (16·37 g., 99%), dissolved in a solution of sodium (6 g.) in oxygen-free benzyl alcohol (75 ml.) and kept

at 25° for 4 days (cf. Levene and Raymond, *J. Biol. Chem.*, 1932, **97**, 751). After acidification with 20% acetic acid (200 ml.) the 6-*O*-benzyl ether was isolated as described above and distilled at 180—190° (bath-temp.)/0·1 mm. The product (7·69 g., 46·5%), n_D^{19} 1·5070, $[\alpha]_D^{21}$ −37° (*c*, 2 in $CHCl_3$), was clearly identical with the benzyl ether described above (Found: C, 63·2; H, 7·8%).

Hydrolysis of 6-O-*benzyl*-3-O-*methyl*-1 : 2-O-iso*propylidene*-α-D-*glucose*. The above derivative (18·63 g.) was refluxed in dioxan (150 ml.) and 0·2N-sulphuric acid (150 ml.) until its rotatory power was constant {$[\alpha]_D^{20}$ +21·6° (15 min.) ⟶ +36·7° (1 hr.)}. After neutralisation with barium carbonate the solution was filtered, adjusted to pH 5·5 with acetic acid, and evaporated to dryness, yielding 6-O-*benzyl*-3-O-*methyl*-D-*glucose* as a colourless syrup (16·05 g., 98%), $[\alpha]_D^{20}$ +38° (*c*, 1·5 in EtOH) (Found: C, 58·8; H, 7·6. $C_{14}H_{20}O_6$ requires C, 59·1; H, 7·1%). This gave a single spot on paper chromatography [R_F 0·71 in butanol–light petroleum (b. p. 80—100°), (1 : 1), saturated with water]. The *phenylosazone* had m. p. 137—139° (from aqueous ethanol) (Found: N, 12·0. $C_{26}H_{30}O_4N_4$ requires N, 12·1%). The same osazone was obtained from material whether prepared by route (a) or route (b).

Action of Lime-water on 6-O-*Benzyl*-3-O-*methyl*-D-*glucose*.—(*a*) A solution of the glucose derivative in oxygen-free lime-water (50 ml.; 0·04N) was kept at 25° under nitrogen and the formation of saccharinic acid followed as in the case of 3-*O*-methyl-D-glucose (Part III, *loc. cit.*):

Time (hr.)	1·0	4·0	7·0	100	150	200	250
Sacc. acid (equiv./mole)	0·12	0·41	0·575	0·90	0·98	0·99	0·99

Paper-chromatographic analysis of intermediate fractions (solvent as above) showed the slow disappearance of the glucose derivative accompanied by the formation of an acid (R_F <0·05) and the intermediate formation of a ketose (R_F 0·72), probably 6-*O*-benzyl-3-*O*-methyl-D-fructose.

(*b*) A solution of 6-*O*-benzyl-3-*O*-methyl-D-glucose (16·05 g.) in oxygen-free water (400 ml.) was treated with calcium hydroxide (15 g.) with occasional shaking at 35° for 4 days. The resulting solution was filtered from excess of calcium hydroxide, saturated with carbon dioxide, boiled for a few minutes, and again filtered. The filtrate was evaporated to dryness, to yield the mixed calcium 6-*O*-benzyl-D-glucometasaccharinates as a pale yellow syrup (12·77 g., 78%). These were dissolved in warm ethanol (100 ml.) and kept at room temperature overnight; the β-*isomer* separated (8·07 g.). After crystallisation, from hot water, in fine colourless needles it had $[\alpha]_D^{20}$ −6·5° (*c*, 3 in H_2O) (Found: C, 53·6; H, 6·3; Ca, 6·8. $C_{13}H_{17}O_6Ca_{\frac{1}{2}}$ requires C, 53·9; H, 5·9; Ca, 6·9%). The crude α-isomer (4·50 g.) obtained by evaporation of the mother-liquors from the above reaction, was dissolved in ethanol (50 ml.) and water (10 ml.). Fractional precipitation by ether ultimately yielded pure *calcium* 6-O-*benzyl*-α-D-*glucometasaccharinate* as a white powder, $[\alpha]_D^{20}$ −1·8° (*c*, 4 in H_2O) (Found: C, 63·2; H, 7·8; Ca, 7·4%).

In later experiments yields of up to 95% of the crude mixture of calcium salts were obtained and this material was suitable for the next stage.

5-O-*Benzyl*-2-*deoxy*-D-*ribose*.—Barium acetate (0·40 g.) and ferric sulphate (0·20 g.) were added to a solution of the mixed calcium salts (4·35 g. from the previous reaction) in water (50 ml.). Hydrogen peroxide (2·5 ml.; 30%) was added to the boiled and filtered mixture after cooling to 40° and the resulting solution was then warmed to 60° to initiate the reaction. When this had subsided and the temperature of the solution had fallen to 40°, more hydrogen peroxide (2·5 ml.) was added and the procedure repeated. The resultant solution was filtered and extracted with ether (5 × 25 ml.), and the extracts were dried (Na_2SO_4) and evaporated to dryness to yield 5-O-*benzyl*-2-*deoxy*-D-*ribose* as a colourless syrup (0·701 g.), $[\alpha]_D^{20}$ +9·4° (*c*, 4 in EtOH) (Found: C, 64·8; H, 7·2. $C_{12}H_{16}O_4$ requires C, 64·3; H, 7·2%). Continuous extraction of the residual aqueous solution with ether for 24 hr. yielded a further quantity (0·880 g., total 47%) of the same compound (Found: C, 64·7; H, 7·5%), and the product from both extractions gave only a single spot on paper chromatography (R_F 0·78; solvent as above).

5-*O*-Benzyl-2-deoxy-D-ribose (2·23 g.) and toluene-ω-thiol (3 ml.) were cooled to 0°, mixed with concentrated hydrochloric acid (6 ml.), and shaken at room temperature for 30 min. The resultant emulsion was diluted with chloroform (50 ml.) and poured into water (50 ml.), the chloroform extract being subsequently washed with saturated sodium hydrogen carbonate solution and then with water, dried (Na_2SO_4), and evaporated to dryness. 5-O-*Benzyl*-2-*deoxy*-D-*ribose dibenzyl mercaptal* crystallised slowly on trituration with ether–light petroleum and when recrystallised from a mixture of the same solvents had m. p. 71—71·5°, $[\alpha]_D^{20}$ +3·1° (*c*, 3 in $CHCl_3$) (4·11 g., 91%) (Found: C, 68·4; H, 6·6; S, 13·8. $C_{26}H_{30}O_3S_2$ requires C, 68·7; H, 6·7; S, 14·1%).

Preparation of 3 : 5-O-*Benzylidene*-2-*deoxy*-D-*ribose*.—4 : 6-O-*Benzylidene*-3-O-*methyl*-D-*glucose*. 3-*O*-Methyl-D-glucose (20·0 g.; Glen, Myers, and Grant, *J.*, 1951, 2568) was shaken in nitrogen with freshly distilled benzaldehyde (50 ml.) and powdered zinc chloride (18 g.) for 24 hr., and the resulting solution poured into ice-water (200 ml.) and stirred vigorously for 10 min. After decantation of the aqueous solution the amorphous precipitate was triturated with light petroleum (100 ml.; b. p. 60—80°), filtered, and washed repeatedly with light petroleum until free from the odour of benzaldehyde, and with ice-water until the washings were free from chloride ions. The *product*, dried over phosphoric oxide (yield, 12·3 g., 42%), had m. p. 128—132°, and, after one crystallisation from methanol–water, m. p. 130—133°, $[\alpha]_D^{20}$ +55° ⟶ +16° (7 days; *c*, 1 in MeOH) (Found: C, 59·3; H, 6·5; OMe, 11·1. $C_{14}H_{18}O_6$ requires C, 59·5; H, 6·4; OMe, 11·0%). The 2 : 4-*dinitrophenylhydrazone* was prepared by boiling a solution of the glucose derivative (0·56 g.) in ethanol (15 ml.) with powdered 2 : 4-dinitrophenylhydrazine (0·40 g.) for 1½ hr. After cooling to room temperature and filtration from a small amount of the unchanged base, the hydrazone was precipitated by the addition of water (20 ml.). It separated from ethanol–water as fine yellow needles, m. p. 167—167·5° (Found: N, 12·3; OMe, 6·3. $C_{20}H_{22}O_9N_4$ requires N, 12·1; OMe, 6·7%).

Action of lime-water on 4 : 6-O-*benzylidene*-3-O-*methyl*-D-*glucose*. This sugar (20·15 g.) and calcium hydroxide (20 g.) in oxygen-free water (1 l.) were stirred in a sealed flask at 20° ± 1°. At intervals, samples (5 ml.) of the filtered solution were shaken with Amberlite resin IR-120 (*ca.* 1 g.) and filtered. The filtrate and resin washings (20 ml.) titrated with 0·025*N*-potassium hydroxide furnished the following results:

Time (hr.)	1·3	18	24	95
Acidity (equiv./mole)	0·70	0·81	0·83	0·88

Examination of the resin-treated solution at this stage by paper chromatography (solvent as above) indicated the presence of a ketose (R_F 0·80; staining relatively slowly with alkaline silver nitrate and probably 4 : 6-*O*-benzylidene-3-*O*-methyl-D-fructose), and a trace of the original glucose derivative (R_F 0·76). The filtered solution, after saturation with carbon dioxide, was boiled, filtered again, and concentrated at 40°. The solution (200 ml.) at room temperature overnight deposited fine, white crystals of *calcium* 4 : 6-O-*benzylidene*-3-*deoxy*-D-*mannonate* (6·05 g., 29·5%) which, recrystallised once from hot water, showed $[\alpha]_D^{20}$ −58° (*c*, 1 in H_2O) [Found: C, 53·9; H, 5·4. $(C_{13}H_{15}O_6)_2Ca$ requires C, 54·4; H, 5·3%]. The filtrate was evaporated to a yellow syrup which crystallised on trituration with warm acetone, the acetone extract yielding on evaporation a brown syrup (0·44 g.) which was not examined further.

Part of the mixed calcium salts (5·05 g. from 13·09 g.; 64%) was dissolved in hot ethanol (30 ml.); fractional precipitation by ether then yielded *calcium* 4 : 6-O-*benzylidene*-3-*deoxy*-D-*gluconate dihydrate*, $[\alpha]_D^{20}$ −34° (*c*, 1 in H_2O) [Found: C, 50·8; H, 5·6. $(C_{13}H_{15}O_6)_2Ca,2H_2O$ requires C, 51·1; H, 5·6%].

Acidic hydrolysis of calcium 4 : 6-O-*benzylidene*-3-*deoxy*-D-*mannonate*. The mannonate (0·10 g.) was stirred with Amberlite resin IR-120 (1 g.) in water (10 ml.) at 60° for 2 hr., and subsequently filtered and evaporated to dryness. The residue crystallised readily and when recrystallised once from acetone had m. p. 86—88°, alone or in admixture with authentic 3-deoxy-γ-D-mannonolactone (Richards, *loc. cit.*).

3 : 5-O-*Benzylidene*-2-*deoxy*-D-*ribose*. Barium acetate (0·36 g.) and ferric sulphate (0·18 g.) were added to an aqueous solution of the mixed calcium salts of 4 : 6-*O*-benzylidene-3-deoxy-D-mannonic and -gluconic acids (5·05 g.). The solution was then boiled for a few minutes, filtered, cooled to 40°, and treated with hydrogen peroxide (2·5 ml.; 30%), with subsequent warming to initiate the reaction. When the temperature had fallen to 40° more hydrogen peroxide (2·5 ml.) was added and the procedure repeated. The resulting solution was filtered and extracted with ether (2 × 50 ml.), and the extracts were dried (Na_2SO_4) and evaporated, to yield 3 : 5-O-*benzylidene*-2-*deoxy*-D-*ribose* as a colourless syrup (0·771 g.), $[\alpha]_D^{21}$ −61° (*c*, 2 in EtOH) (Found: C, 65·2; H, 6·3. $C_{12}H_{14}O_4$ requires C, 65·0; H, 6·3%). This gave a single spot on paper chromatography (R_F 0·82; solvent as above). Further continuous extraction of the aqueous solution with ether for 24 hr. yielded a further quantity (0·429 g.) of the same compound. More barium acetate (0·2 g.) and ferric sulphate (0·1 g.) were then added to the remaining aqueous solution which was boiled, filtered, and treated with more hydrogen peroxide (2 × 2 ml.) as described above. Continuous extraction of the resulting solution with ether for 24 hr. yielded a further quantity of 3 : 5-*O*-benzylidene-2-deoxy-D-ribose (0·429 g.; total yield 41·8%). The 2 : 4-*dinitrophenylhydrazone* was prepared by boiling an ethanolic solution (10 ml.) of this product (0·32 g.) with 2 : 4-dinitrophenylhydrazine (0·25 g.) for 1 hr. Addition of water precipitated

the hydrazone (0·40 g.) which separated from its ethanol–water solution as fine yellow needles, m. p. 132—134° (Found : N, 14·3. $C_{18}H_{18}O_7N_4$ requires N, 13·9%).

Acid hydrolysis. The ribose derivative (0·090 g.) was stirred with Amberlite resin IR-120 (0·5 g.) in water (10 ml.) at room temperature for 18 hr. and the resulting solution, after filtration, washed with chloroform and evaporated to dryness. The residual syrup was dissolved in methanol (1 ml.) containing freshly distilled aniline (0·02 g.) and the solution heated under reflux for 2 hr. Concentration of the resulting solution then yielded colourless needles of *N*-2-deoxy-D-ribosylaniline, m. p. and mixed m. p. 170—173°.

THE BRITISH RAYON RESEARCH ASSOCIATION, HEALD GREEN LABORATORIES, WYTHENSHAWE, MANCHESTER. [*Received, May 5th,* 1954.]

The Degradation of Carbohydrates by Alkali. Part VIII. Melibiose.*

By W. M. CORBETT and J. KENNER.

[Reprint Order No. 5367.]

The action of lime-water on melibiose is shown to yield lactic acid and galactose, and, by a parallel reaction, galactosyl meta- and *iso*-saccharinic acids. This behaviour is contrasted with that of glucose.

WE now present the results of our study of the action of lime-water on melibiose as a complement to that of Hough, Jones, and Richards (*J.*, 1954, 295) on the behaviour of the disaccharide towards ammonia.

Degradation of this 6-*O*-galactosylglucose by alkali would be expected to correspond to that of glucose itself which, under similar conditions, yields essentially lactic and saccharinic acid. Thus we should have as alternative modes of decomposition :

(*a*) 1 mol. of melibiose ⟶ 2 mols. of lactic acid + 1 mol. of galactose

and

(*b*) 1 mol. of melibiose ⟶ 1 mol. of galactosylsaccharinic acid(s)

whence (on the assumption that galactose is only slowly attacked under the conditions of the experiment at any time), in molar concentrations, lactic acid is equivalent to two galactose molecules, and galactosylsaccharinic acid is equivalent to the melibiose decomposed

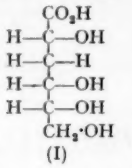
Degradation of melibiose by saturated lime-water at 25°.

Time (hr.)	α_D	Melibiose decompd. (equiv.)	Monoses produced (equiv.)	Lactic acid (calc. equiv.)	Gal.-sacch. acids (calc. equiv.)	Total acid (calc. equiv.)	Total acid (found equiv.)	Substances found on paper
1	+0·16°	0·000	0·000	0·000	0·000	0·000	0·022	Melibiulose
2	0·16	0·000	0·000	0·000	0·000	0·000	0·023	
3	0·16	0·000	0·000	0·000	0·000	0·000	0·053	Galactose
4	0·15	0·000	0·000	0·000	0·000	0·000	0·073	
5	0·15	0·000	0·000	0·000	0·000	0·000	0·102	
6	0·14	0·063	0·063	0·126	0·000	0·126	0·128	
24	0·11	0·218	0·202	0·405	0·016	0·421	0·398	
30	0·11	0·244	0·202	0·405	0·041	0·446	0·499	Acids and tagatose
48	0·10	0·344	0·289	0·577	0·055	0·632	0·648	
54	0·09	0·375	0·256	0·511	0·120	0·631	0·708	
120	0·07	0·525	0·409	0·819	0·116	0·935	0·924	Further acids and talose
144	0·07	0·552	0·427	0·853	0·126	0·975	0·975	
192	Turbid	0·597	0·457	0·917	0·134	1·051	1·043	
216		0·617	0·442	0·917	0·175	1·092	1·108	
288		0·700	0·558	1·118	0·142	1·260	1·202	

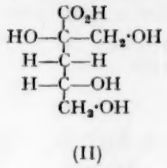
minus the galactose formed. The annexed Table of analytical results shows how, after the early stages of reaction, they broadly confirm this deduction.

* Part VII, preceding paper.

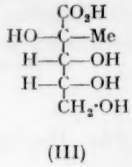
On the other hand, and in striking contrast with the behaviour of glucose, the saccharinic acids obtained from melibiose are essentially of the meta- (I), with some of the *iso*-type (II), whereas the main product of the action of lime-water on glucose is saccharinic acid (III) (Kiliani, *Ber.*, 1882, **15**, 2953). Our findings accord rather with Nef's (*Annalen*, 1910, **376**, 89) on the action of 8N-sodium hydroxide on glucose, which we have interpreted in terms of attack by the alkali on the primary alcoholic group (*J.*, 1954, 3274). This group



(I)



(II)



(III)

is of course not available in melibiose and it will be desirable to ascertain whether other compounds of this type behave similarly.

Experimental

Isolation of the Degradation Products.—A solution [5 l.; $\alpha_D = 2{\cdot}77°$ ($l = 4$) after 5 min.] of melibiose (28·45 g.) in saturated oxygen-free lime-water (0·033N) was kept at approx. 21—22° until the observed optical rotatory power was constant, values being :

Time (days)	1	4	5	6	7	8	11	12	15	19
α_D (4 dm.)	2·27°	1·70°	1·68°	1·44°	1·41°	1·30°	1·20°	1·16°	1·06°	0·98°

The calcium ions were then completely removed by addition of the theoretical amount of oxalic acid before the solution was concentrated under reduced pressure to 100 ml., and exhaustively extracted with ether for 5 days, the extract being kept neutral by the presence of an aqueous suspension of zinc carbonate (Nadeau, Newlin, and Evans, *J. Amer. Chem. Soc.*, 1933, **55**, 4957). Zinc DL-lactate (5·673 g.) was thus obtained and identified by conversion into the (−)-brucine salt, m. p. and mixed m. p. 190—200°. The extracted aqueous solution was filtered from inorganic material and stirred with Amberlite IR-4B resin (50 g.) for 20 hr. After filtration and washing of the resin with water (2 × 100 ml.) concentration of the combined filtrate and washings yielded a syrup (10·705 g.) which was shown by paper chromatography to be essentially a mixture of mono- and di-saccharides; it gave spots of R_F (BuOH–C_5H_5N–H_2O; 6 : 4 : 3) 0·057 (melibiose), 0·10 (melibiulose), 0·21 (galactose), 0·255, 0·31, 0·34, and 0·39 (tagatose, talose, sorbose ?), 0·49, 0·55, and 0·70 (saccharins). The resin was then stirred for 24 hr. with 0·1M-sodium carbonate (400 ml.), filtered, and washed with water (2 × 100 ml.), and the combined filtrate and washings were then stirred for a further 24 hr. with Amberlite IR-120 resin (100 g.). After filtration the resin was washed with water (2 × 100 ml.), the combined filtrate and washings were concentrated under reduced pressure to a syrup (3·862 g.) and neutralised with lime-water. Concentration afforded the amorphous calcium salts (4·023 g.).

After these had been heated with water (7 ml.) the mixture was cooled and filtered, to give an insoluble calcium salt (0·812 g.) of which a sample (0·148 g.) gave brucine DL-lactate (0·608 g.), m. p. and mixed m. p. 190—200°, $[\alpha]_D^{24}$ −35·4° (*c*, 2 in H_2O). Alcohol was added in portions to the filtrate to give fractions : (*a*) (from 59% ethanol) white amorphous powder (1·205 g.), $[\alpha]_D^{22}$ +58·6° (*c*, 1·01 in H_2O) ⟶ +68·7° (*c*, 0·80 in H_2O, corrected for removal of calcium ions) on treatment with Amberlite IR-120 resin; (*b*) (from 72% ethanol) white amorphous powder (0·310 g.), $[\alpha]_D^{22}$ +65·2° (*c*, 1·10 in H_2O) ⟶ +68·8° (*c*, 0·99 in H_2O) (Found : C, 39·0; H, 6·7. Calc. for $C_{24}H_{42}O_{22}Ca$: C, 39·9; H, 5·9%); (*c*) (from 85% ethanol) straw-coloured amorphous powder (0·077 g.), $[\alpha]_D^{21}$ +72·6° (*c*, 0·77 in H_2O), and (*d*) straw-coloured amorphous powder (0·228 g.), $[\alpha]_D^{21}$ +66·3° (*c*, 0·77 in H_2O). These fractions proved to contain mixtures of 6-*O*-galactopyranosylsaccharinic acids. Thus, when a sample of fraction (*a*) (0·767 g.) in water (50 ml.) was heated with Amberlite IR-120 resin (5 g.) at 75° for 120 hr. the following periodical observations were made :

Time (hr.)	0	1	20	26	43	49	100	120
α_D (2 cm.)	1·81°	1·80°	1·75°	1·73°	1·66°	1·64°	1·51°	1·34°

Paper chromatography with butanol–water–acetic acid (4 : 2 : 1) followed by the hydroxylamine–ferric chloride spray of Abdel Akher and Smith (*J. Amer. Chem. Soc.*, 1951, **73**, 5859) then

yielded two main spots, with R_F 0·19 and 0·29 (cf. authentic β-metasaccharin 0·28), and faint spots with R_F 0·35 and 0·43 (cf. authentic α-*iso*saccharin 0·37). With butanol–pyridine–water (6 : 4 : 3) (silver nitrate spray; Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444) the main components had R_F 0·17 (authentic galctose 0·17) 0·53, 0·65 (authentic β-metasaccharin 0·62), 0·70 (authentic α-*iso*saccharin 0·68), 0·76 (authentic saccharin 0·74), and 0·80, with streaks of approx. values 0·29 and 0·37. The filtered solution was concentrated, and the residue dried at 45°/0·01 mm. for 1 hr. (0·651 g.) and extracted with dry acetone. The acetone-insoluble residue (0·250 g.) was shown by paper-chromatography to be essentially galactose and from it was prepared galactosazone, m. p. and mixed m. p. 193—195°. The syrup (0·276 g.) obtained by concentration of the acetone extract was essentially a mixture of saccharins.

An aqueous solution of the mixture (0·241 g.) was heated on a boiling-water bath for 1 hr. with excess of brucine, cooled, filtered, and concentrated to a syrup (0·768 g.) which slowly crystallised to give a white product (0·201 g. from 0·536 g.). It was essentially brucine α-metasaccharinate, m. p. 110—127°, $[\alpha]_D^{20}$ −30·5° (*c*, 0·786 in H_2O), and when its aqueous solution was stirred with Amberlite IR-120 (H) resin it gave a lactone, $[\alpha]_D^{20}$ +22·5° (*c*, 0·222 in H_2O). Nef (*loc. cit.*) gives m. p. 145—150°, $[\alpha]_D$ −23·1° and $[\alpha]_D^{20}$ +25·3° for brucine α-metasaccharinate and α-metasaccharin respectively.

Determination of the Degradation Products.—A solution (100 ml.) of melibiose (0·8704 g.) in saturated oxygen-free lime-water (0·0313N) was kept at 25°. Samples (2 ml.) were withdrawn periodically and run into excess of 0·01N-sulphuric acid (10 ml.). After the solution had been titrated with 0·01N-sodium hydroxide (phenolphthalein), it was made up to 50 ml., the optical rotatory power was observed, and the mono- and di-saccharides were estimated in samples of 1 ml. by the charcoal–Celite column method (Corbett, *Chem. and Ind.*, 1953, 1285). Samples of the neutralised solutions were submitted to paper chromatography with butanol–pyridine–water (6 : 4 : 3) (silver nitrate and naphtharesorcinol sprays for development; Hough, Jones, and Wadman, *J.*, 1950, 1702). As above, the ketoses were identified by the latter spray and by comparison of their R_F values with those of the corresponding aldoses. The results are shown on p. 3281.

We are indebted to Dr. E. J. Bourne for a sample of melibiose.

THE BRITISH RAYON RESEARCH ASSOCIATION, HEALD GREEN LABORATORIES,
WYTHENSHAWE, MANCHESTER. [*Received, May 5th*, 1954.]

2-*Mercaptoglyoxalines. Part VIII.* The Preparation of 2-Mercaptoglyoxalines from Glutamic Acid.*

By R. A. F. BULLERWELL, ALEXANDER LAWSON, and H. V. MORLEY.

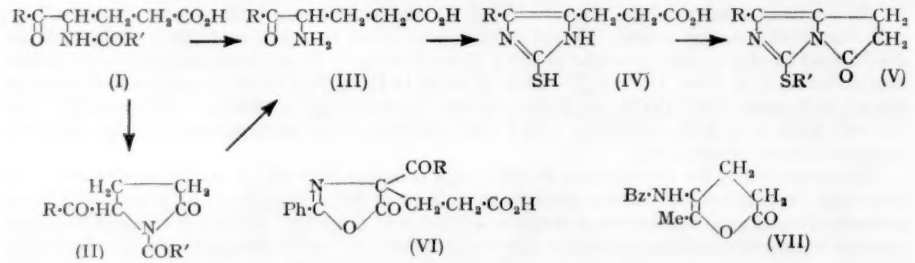
[Reprint Order No. 5373.]

Benzoylglutamic acid has been acylated by several acid anhydrides in the presence of a basic catalyst (Dakin and West, *J. Biol. Chem.*, 1928, **78**, 745). Acylation precedes the formation of the pyrrolidone (II) which on hydrolysis gives the amino-ketone from which the corresponding 2-mercaptoglyoxaline (IV) is obtained by means of thiocyanate. Under certain conditions the reduction of ethyl glutamate according to the Akabori procedure leads to a product which on treatment with thiocyanate gives a 2-mercaptoglyoxaline which is either 1 : 4- or 1 : 5-disubstituted.

THE reaction of glutamic acid with acetic anhydride in the presence of pyridine was shown by Dakin and West (*J. Biol. Chem.*, 1928, **78**, 745) to yield only 15—20% of one molecular equivalent of carbon dioxide. King and McMillan (*J. Amer. Chem. Soc.*, 1952, **74**, 2859) showed that the ω-carboxyl group of the amino-acid caused pyrrolidone ring-closure, 1 : 5-diacetyl-2-pyrrolidone, 1-acetyl-5-oxopyrrolidine-2-carboxylic acid and 3 : 5 : 8 : 10-tetraketoperhydrodipyrrolo[*a*,*d*]pyrazine being isolated. The formation of the last two compounds accounts for the low yield of carbon dioxide and consequently of ketone.

* Part VII, *J.*, 1953, 1046.

As in the case of aspartic acid (Lawson, *J.*, 1953, 1046), by the use of the benzoyl derivative instead of the free amino-acid, one molecular equivalent of carbon dioxide and simultaneous high yields of ketone have been obtained. It was found that decarboxylative acetylation in the presence of pyridine, 2-picoline, or sodium acetate occurred even at 0°, when the crystalline product isolated was 4-benzamido-5-oxohexanoic acid (I; R = Me, R′ = Ph). At 110°, the product was shown to be 5-acetyl-1-benzoyl-2-pyrrolidone (II; R = Me, R′ = Ph), which was also obtained from I; R = Me, R′ = Ph by hot acetic anhydride and pyridine, both the dehydrating and basic reagents apparently being necessary.



The pyrrolidone structure (II) was substantiated as King and MacMillan (*loc. cit.*) did that of 1 : 5-diacetyl-2-pyrrolidone (II; R = R′ = Me). The substance was neutral but slowly absorbed one equivalent of alkali when titrated to phenolphthalein. An acetyl group was indicated by a positive iodoform test, and a monosemicarbazone was prepared. These observations exclude the oxazolone (VI) and the lactone structure (VII).

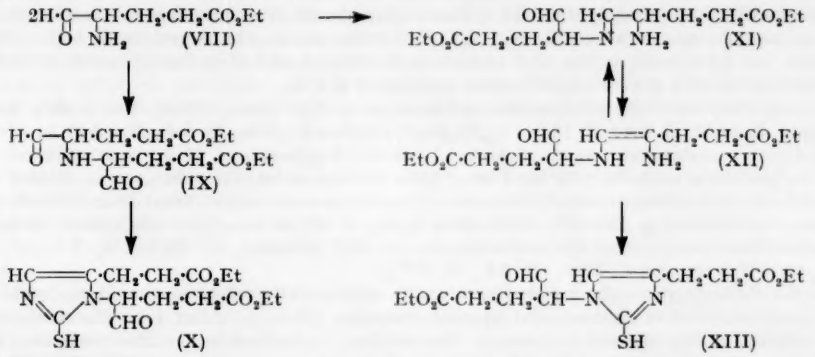
Unsuccessful attempts were made to prepare 1-benzoyl-2-oxopyrrolidine-5-carboxylic acid in order to ascertain whether it also underwent decarboxylative acetylation. Even without such evidence, however, isolation of the benzamido-ketone (I; R = Me, R′ = Ph) at 0° eliminates the possibility of intermediate pyrrolidone formation before *C*-acetylation of benzoylglutamic acid. Further work is being carried out to discover how far our observations are consistent with Cornforth and Elliot's view (*Science*, 1950, **112**, 534) that ketone synthesis occurs by acetylation of an oxazolone.

By employing propionic, butyric, hexanoic, and benzoic anhydrides in place of acetic, analogous pyrrolidones (II) were obtained, but in lower yield. The amino-ketones (III) obtained by hydrolysis of some of the corresponding pyrrolidones were condensed with thiocyanate, to give the 2-mercaptoglyoxalines (IV).

Reducing diethyl glutamate with sodium amalgam at pH 2—2·5 and without delay boiling the resulting solution of the amino-aldehyde (III; R = H) with potassium thiocyanate (cf. Bullerwell and Lawson, *J.*, 1951, 3030) gave β-(2-mercapto-5-glyoxalinyl)-propionic acid (IV; R = H). The action of hot acetic anhydride then produced an acetyl-anhydro-derivative (V; R = H, R′ = Ac) which was rapidly hydrolysed by hot water with loss of the acetyl group. Relatively prolonged boiling with water was required to reconvert the anhydro-compound (V; R = R′ = H) into the 2-mercaptoglyoxalinylpropionic acid. The formation of an *S*-acetyl derivative of a 2-mercaptoglyoxaline having a labile acetyl group has been reported by Heath, Lawson, and Rimington (*J.*, 1951, 2219). Cook, Downer, and Heilbron (*J.*, 1948, 1262) prepared a diacetyl derivative of 5-benzamido-2-mercaptoglyoxaline, thus demonstrating that the ring is capable of accommodating *S*- and *N*-acyl groups simultaneously. This evidence is the basis for the glyoxalino-pyrrolidone structure (V).

When, however, diethyl glutamate was reduced with sodium amalgam at pH 3—5 and the resulting solution kept for some time before the addition of thiocyanate, two neutral substances (separated by benzene) were obtained, both being 2-mercaptoglyoxalines as shown by their reactions with sulphur dioxide and gold chloride and by their high-intensity absorption at 258 mμ. The less-soluble substance, $C_8H_{12}O_2N_2S$, gave on hydrolysis β-(2-mercapto-5-glyoxalinyl)propionic acid (IV; R = H) and was, therefore, the ethyl ester

of (IV; R = H). The benzene-soluble product, $C_{15}H_{22}O_5N_2S$, produced in variable yield, gave aldehydic reactions and lost on hydrolysis two ethyl groups, to give the corresponding aldehydo-dicarboxylic acid. This substance was therefore ethyl β-[1-(3-ethoxycarbonyl-1-formylpropyl)-2-mercapto-5-glyoxalinyl]propionate (X) or the isomer (XIII) depending on whether the original aldehyde (VIII) lost ammonia to give the secondary amino-aldehyde (IX) or lost water to give the Schiff's base (XII). The former seems probable since Siegfried



(*Z. physiol. Chem.*, **1906**, **73**, 196, 201) showed that iminodiacetic acid is formed from glycine by mercuric chloride solution at 40° and Fischer (*Ber.*, **1893**, **26**, 194) observed the production of ammonia from aminoacetaldehyde in slightly acid solution. On the other hand, the conditions do not exclude the formation of a Schiff's base, which might condense with thiocyanate as does *o*-phenylenediamine (Frerichs and Hupka, *Arch. Pharm.*, **1903**, **241**, 165).

A number of other amino-acid esters, in particular alanine ethyl ester, when reduced under less acid conditions than usual, give analogous glyoxalines with an aldehyde-containing substituent and further work is in progress.

Experimental

*Benzoyl-*DL*-glutamic Acid.*—The following modification of Fischer's method (*Ber.*, **1899**, **32**, 2464) was advantageous. DL-Glutamic acid (10 g.) was dissolved in water (150 ml.) containing sodium hydrogen carbonate (50 g.). Benzoyl chloride (22 ml.) was added dropwise with vigorous stirring during 45 min. Stirring was continued for a further 30 min., and the filtered solution was acidified with concentrated hydrochloric acid (58 ml.) without cooling, and again filtered quickly to remove benzoic acid, then kept at 0°. The crude product which separated was dried at 80° for 3 hr. and extracted with light petroleum (b. p. 100—120°) to remove final traces of benzoic acid. Recrystallisation from water gave benzoyl-DL-glutamic acid monohydrate, m. p. 98°, which was converted into the anhydrous acid (13·0 g.; m. p. 152—154°) by heating it at 80°.

*Benzoyl-*DL*-glutamic Anhydride.*—Benzoyl-DL-glutamic acid (5 g.) was warmed with acetic anhydride (20 ml.) on the steam-bath for 15 min. The solution so obtained was cooled and large prisms of the *anhydride* separated. This product was recrystallised from ethyl acetate (Found: C, 61·8; H, 4·6. $C_{12}H_{11}O_4N$ requires C, 61·9; H, 4·7%).

5-Oxopyrrolidine-2-carboxylic Acid.—DL-Glutamic acid (10 g.) heated at 150—160° in a stream of nitrogen for 3 hr. gave 5-oxopyrrolidine-2-carboxylic acid, m. p. 180—183° (from water). DL-Benzoylglutamic acid was heated in the same way for 6 hr. The residue was dissolved in water and the solution extracted with ether to remove benzoic acid. After concentration, 5-oxopyrrolidine-2-carboxylic acid (identified by mixed m. p.) separated. This acid, benzoylated as described above, gave DL-benzoylglutamic acid.

5-Acetyl-1-benzoyl-2-pyrrolidone.—Benzoyl-DL-glutamic acid (3 g.), anhydrous pyridine (10 ml.), and freshly distilled acetic anhydride (10 ml.) were heated at 110° for 45 min. Evolution of carbon dioxide (determined as barium carbonate) was quantitative. The solution was then concentrated under reduced pressure to a semi-solid mass which crystallised upon trituration with ethanol to give *5-acetyl-1-benzoyl-2-pyrrolidone* (2·5 g., 90%), m. p. 148° (from water or

ethyl acetate) (Found: C, 67·3; H, 5·5; N, 5·0. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·6; N, 6·1%). The same product was obtained by using benzoylglutamic anhydride in place of the acid, but there was no advantage in this modification.

Refluxing benzoylglutamic acid (2·5 g.), anhydrous sodium acetate (1·6 g.), and acetic anhydride (20 ml.) for 30 min., gave 5-acetyl-1-benzoyl-2-pyrrolidone in 65% yield. The mother-liquor was then poured into water; benzoic acid (0·4 g.) slowly separated.

5-Acetyl-1-benzoyl-2-pyrrolidone dissolved in hot water to form a neutral solution. On titration with alkali (phenolphthalein) it slowly reacted with one equivalent in a similar manner to a lactone (Found: equiv., 227. $C_{13}H_{13}O_3N$ requires equiv., 231 as monobasic acid). When refluxed for 1 hr. with excess of 0·1N-sodium hydroxide and then back-titrated with 0·1N-hydrochloric acid, it gave a saponification equivalent of 114.

5-Acetyl-1-benzoyl-2-pyrrolidone semicarbazone, m. p. 229° (from water), was readily formed (Found: C, 58·5; H, 5·4; N, 19·3. $C_{14}H_{16}O_3N_4$ requires C, 58·3; H, 5·6; N, 19·4%).

4-Amino-5-oxohexanoic Acid.—5-Acetyl-1-benzoyl-2-pyrrolidone (1 g.) was refluxed with 20% hydrochloric acid (25 ml.) for 1 hr. After cooling in ice, the solution was filtered from benzoic acid and concentrated to dryness. The residue was recrystallised from ethanol–ether to give a product m. p. 60—65°, which after drying at 60° *in vacuo* over phosphoric oxide was *4-amino-5-oxohexanoic acid hydrochloride*, m. p. 162° (Found: C, 39·5; H, 7·0; N, 7·7. $C_6H_{11}O_3N,HCl$ requires C, 39·7; H, 6·6; N, 7·7%).

3 : 6-Dimethylpyrazine-2 : 5-dipropionic Acid.—4-Amino-5-oxohexanoic acid hydrochloride (1 g.) was dissolved in concentrated aqueous ammonia (20 ml.). After 1 hr. the solution was concentrated to dryness under vacuum. The residue, crystallised from water containing a few drops of acetic acid, gave 3 : 6-dimethylpyrazine-2 : 5-dipropionic acid, m. p. 211—213° (Found: C, 57·4; H, 7·35. Calc. for $C_{12}H_{16}O_4N_2$: C, 57·1; H, 6·35%).

β-(2-Mercapto-4-methyl-5-glyoxalinyl)propionic Acid.—Crude 4-amino-5-oxohexanoic acid hydrochloride obtained from 5-acetyl-1-benzoyl-2-pyrrolidone (2 g.) was dissolved in water (10 ml.) together with potassium thiocyanate (1 g.) and was heated on the steam-bath until crystals separated. After recrystallisation from water the *propionic acid* (0·9 g.) had m. p. 268° (Found: C, 44·7; H, 5·4; N, 15·2. $C_7H_{10}O_2N_2S$ requires C, 45·1; H, 5·4; N, 15·1%).

4-Benzamido-5-oxohexanoic Acid.—Benzoyl-DL-glutamic acid (4·5 g.), acetic anhydride (10 ml.), and 2-picoline (5 ml.) were shaken at room temperature until all went into solution, which was then stored at 0° for 24 hr. Crushed ice was added, followed by 17·5% hydrochloric acid until acid to Congo-red (final vol. of solution, 60 ml.). Overnight *4-benzamido-5-oxohexanoic acid* (2·7 g.) separated. Recrystallised from ethyl acetate it had m. p. 152—153° (Found: C, 62·3; H, 5·8; N, 6·5. $C_{13}H_{15}O_4N$ requires C, 62·7; H, 6·0; N, 5·6%). The *semicarbazone* had m. p. 212° (from water) (Found: C, 54·1; H, 5·9; N, 17·4. $C_{14}H_{18}O_4N_4$ requires C, 54·9; H, 5·9; N, 18·3%).

1-Benzoyl-5-propionyl-2-pyrrolidone.—Benzoyl-DL-glutamic acid (3 g.), propionic anhydride (12 ml.), and pyridine (10 ml.) were refluxed together for 45 min. The solution was then concentrated to a syrup under vacuum. Ethanol (5 ml.) was added and, after concentration again, the residue was dissolved in hot ethyl acetate. During 1 week at 0°, *1-benzoyl-5-propionyl-2-pyrrolidone* (2·2 g.), m. p. 104° (from ethanol), separated (Found: C, 68·1; H, 6·3. $C_{14}H_{15}O_3N$ requires C, 68·6; H, 6·1%). The *semicarbazone*, recrystallised from water, had m. p. 201° (Found: C, 59·8; H, 6·1. $C_{15}H_{18}O_3N_4$ requires C, 59·6; H, 6·0%).

β-(4-Ethyl-2-mercapto-5-glyoxalinyl)propionic Acid.—1-Benzoyl-5-propionyl-2-pyrrolidone (2 g.) was refluxed with 20% hydrochloric acid (50 ml.) for 1 hr. The solution was cooled, filtered, and concentrated to dryness. The residue was washed with ether and dissolved in water (10 ml.). Potassium thiocyanate (2 g.) was added in three portions during 2 hours' heating on the steam-bath. The product, recrystallised from water, gave the *glyoxalinylpropionic acid* (0·6 g.), m. p. 229—230° (Found: C, 48·6; H, 6·0. $C_8H_{12}O_2N_2S$ requires C, 48·0; H, 6·0%).

1-Benzoyl-5-butyryl-2-pyrrolidone.—Benzoyl-DL-glutamic acid (5 g.), butyric anhydride (20 ml.) and 2-picoline (15 ml.) were heated for 1 hr. at 110°, then concentrated at 0·1 mm. The residue was dissolved in ether (50 ml.) and the solvent was allowed to evaporate at room temperature. *1-Benzoyl-5-butyryl-2-pyrrolidone* (1·6 g.) separated and after recrystallisation from water had m. p. 67° (Found: C, 69·8; H, 6·9. $C_{15}H_{17}O_3N$ requires C, 69·5; H, 6·6%).

β-(2-Mercapto-4-propyl-5-glyoxalinyl)propionic Acid.—1-Benzoyl-5-butyryl-2-pyrrolidone (0·5 g.) was refluxed with 20% hydrochloric acid (25 ml.) for 2 hr. The amino-ketone obtained was treated with potassium thiocyanate (1 g.) and *β-(2-mercapto-4-propyl-4-glyoxalinyl)propionic acid*, m. p. 217°, was obtained as above (Found: C, 51·0; H, 6·7. $C_9H_{14}O_2N_2S$ requires C, 50·5; H, 6·5%).

1-*Benzoyl-5-hexanoyl-2-pyrrolidone*.—Benzoyl-DL-glutamic acid (2 g.), hexanoic anhydride (8 ml.), and 2-picoline (8 ml.) were heated for 2 hr. at 120°. After cooling, ethanol (10 ml.) was added and the solution kept overnight. Solvents were removed at 0·1 mm Water (40 ml.) was added to the oily residue and the liquid was made just alkaline by addition of solid sodium hydrogen carbonate. The insoluble oil crystallised, to give 1-*benzoyl-5-hexanoyl-2-pyrrolidone* (0·7 g.), m. p. 83—84° (from water) (Found: C, 71·1; H, 7·4. $C_{17}H_{21}O_3N$ requires C, 71·1; H, 7·3%).

1 : 5-*Dibenzoyl-2-pyrrolidone*.—Benzoyl-DL-glutamic acid (2·5 g.), benzoic anhydride (5 g.), and 2-picoline (10 ml.) were heated at 90—100° for 1½ hr., then poured into water (100 ml.) which was then acidified to Congo-red with dilute hydrochloric acid. The precipitate was washed with sodium hydrogen carbonate solution to remove benzoic acid, and the residue, after being washed with water and then ethanol, consisted of 1 : 5-*dibenzoyl-2-pyrrolidone* (0·75 g.). Recrystallised from ethanol it had m. p. 167° (Found: C, 74·1; H, 5·4. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·2%).

β-(2-*Mercapto-4-glyoxalinyl*)*propionic Acid*.—By Bullerwell and Lawson's method (*J.*, 1951, 3031), diethyl DL-benzoylglutamate (from DL-glutamic acid, 10 g.) was reduced at pH 2·3 and 0° by sodium amalgam (2·3%; 400 g.). Subsequent condensation with potassium thiocyanate (12 g.) gave β-(2-mercapto-4-glyoxalinyl)propionic acid (4·1 g., 35%), m. p. 203—205° (from water).

2′-*Mercaptoglyoxalino*(1′ : 5′-1 : 5)*pyrrolid-2-one*.—β-(2-Mercapto-4-glyoxalinyl)propionic acid (1 g.) was dissolved in boiling acetic anhydride (10 ml.). On cooling, 2′-*acetylthioglyoxalino*-(1′ : 5′-1 : 5)*pyrrolid-2-one* separated. Recrystallised from ethyl acetate it had m. p. 192° (Found: C, 49·4; H, 4·3. $C_8H_8O_2N_2S$ requires C, 49·0; H, 4·1%).

This was rapidly crystallised from boiling water, the clear solution being chilled in ice. 2′-*Mercaptoglyoxalino*(1′ : 5′-1 : 5)*pyrrolid-2-one*, m. p. 228°, separated (Found: C, 47·0; H, 4·4. $C_6H_6ON_2S$ requires C, 46·8; H, 3·9%).

β-(2-*Mercapto-4-glyoxalinyl*)*propionamide*.—2′-Acetylthioglyoxalino(1′ : 5′-1 : 5)pyrrolid-2-one (1 g.) was shaken with concentrated ammonia solution (10 ml.) until all went into solution. After 1 hr., the solution was evaporated to dryness *in vacuo*, and the residue was recrystallised from water containing a few drops of acetic acid. The *propionamide* (0·75 g.) so obtained had m. p. 210° (Found: C, 42·9; H, 5·4; N, 24·3. $C_6H_9ON_3S$ requires C, 42·1; H, 5·3; N, 24·6%).

Reduction of Diethyl Glutamate at pH 3—5.—Reduction of the ester (25 g.) with sodium amalgam (600 g.; 2·5%) was carried out as previously described, except that the pH was maintained between 3 and 5. When all the amalgam had been added, the solution was kept at pH 4·0 for 1 hr. at room temperature before being boiled with ammonium thiocyanate (33 g.) for 0·5 hr., then kept overnight at 0°; the crystals were filtered off, dried, and extracted with benzene. The residue, recrystallised from ethanol, gave colourless needles of *ethyl* β-(2-*mercapto-5-glyoxalinyl*)*propionate* (8·5 g.), m. p. 151° (Found: C, 48·3; H, 6·4. $C_8H_{12}O_2N_2S$ requires C, 48·1; H, 6·6%). Hydrolysis with concentrated hydrochloric acid gave 2-mercaptoglyoxalinylpropionic acid. On concentration of the benzene extract and addition of light petroleum (b. p. 60—80°), there were deposited, at 0°, colourless needles of *ethyl* β-1-(3-*ethoxycarbonyl*-1-*formylpropyl*)-2-*mercapto*-4- or -5-*glyoxalinylpropionate*, m. p. 99—100° (maximum yield, 3·3 g.) (Found: C, 52·5; H, 6·4; N, 8·2; S, 9·5. $C_{15}H_{22}O_5N_2S$ requires C, 52·6; H, 6·4; N, 8·2; S, 9·3%). The 2 : 4-*dinitrophenylhydrazone*, prisms from toluene, had m. p. 144° (Found: C, 48·9; H, 4·9. $C_{21}H_{26}O_8N_6S$ requires C, 48·2; H, 5·0%). This ester (0·3 g.) was hydrolysed by cold 3N-sodium hydroxide (10 ml.) for 24 hr. Addition of concentrated hydrochloric acid to pH 4, and recrystallisation of the precipitate from water gave light yellow needles of β-1-(3-*carboxy*-1-*formylpropyl*)-2-*mercapto*-4- or -5-*glyoxalinylpropionic acid*, m. p. 227—228° (0·12 g.) (Found: C, 45·4; H, 5·1; N, 9·8; S, 11·4. $C_{11}H_{14}O_5N_2S$ requires C, 46·2; H, 4·9; N, 9·8; S, 11·2%).

We thank Mr. J. O. Stevens for technical assistance.

ROYAL FREE HOSPITAL SCHOOL OF MEDICINE,
8 HUNTER STREET, LONDON, W.C.1.

[*Received, May 7th,* 1954.]

The Structure of Overcrowded Aromatic Compounds. Part I. A Preliminary Survey.

By E. Harnik, F. H. Herbstein, G. M. J. Schmidt, and (in part) F. L. Hirshfeld

[Reprint Order No. 5059.]

The configurations of compounds showing " intramolecular overcrowding " cannot be predicted by conventional methods owing to lack of data on the effects of repulsion between non-bonded atoms. Where such repulsion leads to observable deformation of an aromatic system, the distorted molecule may provide information about the nature of interatomic repulsion and also about the manner in which the aromatic system reacts to mechanical stresses. Four groups of overcrowded aromatic structures are considered, and the published data surveyed for an indication of the kinds of distortions observed. Such deviations from the conventional molecular structure include abnormal bond angles and non-planarity of aromatic systems. An approach of 3·0 Å or less between non-bonded carbon atoms frequently results in repulsion forces sufficient to produce detectable distortions within the molecule.

A preliminary crystallographic investigation of several overcrowded compounds has yielded information on their molecular shape, but only complete structure analyses can reveal the nature and extent of the deformations present.

As a result of much work on the structure of organic molecules, mainly by *X*-ray and electron-diffraction methods, and of parallel progress in the theoretical interpretation of the forces responsible for chemical bonding, it has become possible to predict the bond lengths and bond angles of many such molecules with fair accuracy. Nevertheless, it must be recognised that our information on molecular structure is still incomplete since the nature and effect of intramolecular repulsion forces between non-bonded atoms have not yet been investigated systematically. The successful calculation of bond lengths and angles in planar aromatic systems of the type of anthracene, coronene, etc., suggests that in such compounds at any rate these intramolecular repulsion forces can largely be ignored; on the other hand, both chemical and structural evidence has accumulated to demonstrate that in many compounds the influence of these repulsion forces on molecular structure is not negligible. One class of such compounds has been termed " overcrowded " (Bell and Waring, *J.*, 1949, 2689; Harnik, Herbstein, and Schmidt, *Nature*, 1951, **168**, 158). In its wider aspects this phenomenon has been rather loosely ascribed to the operation of " steric effects."

The work described in this and subsequent papers represents a systematic study of overcrowded aromatic compounds in an attempt to close the gap in the experimental data. Part I presents a brief discussion of the information to be sought from such a study and a summary of some already available data as well as the results of an *X*-ray crystallographic survey of a number of overcrowded compounds; Parts II, III, and IV describe the crystallographic analyses of dianthronylidene, 3 : 4-benzophenanthrene, and tetrabenzonaphthalene. The crystal structures of 5 : 4′-dimethyl-3 : 4-benzophenanthrene and of the β-modification of 3 : 4-5 : 6-dibenzophenanthrene will be reported later.

In many aromatic overcrowded molecules the compression of non-bonded atoms may be partly relieved through the adoption by the aromatic system of a non-planar configuration. Such molecules are of interest in that they permit a direct observation of the equilibrium between interatomic repulsion and the chemical forces tending to maintain planarity. Thus we may hope, on the one hand, for information about the nature of short-range repulsion forces between non-bonded atoms, which should be useful for an understanding of steric influences in general. On the other hand, the organic chemist may expect information about the manner in which a conjugated molecule reacts to static mechanical stresses. Thus, where measurable distortions are produced by repulsion forces in an overcrowded compound, the distorted molecule, regarded as an elastic mechanical system, permits a

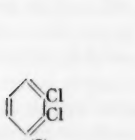
direct intercomparison of the bending force constants of the distorted bonds. These force constants which, except in fairly simple molecules, cannot be derived from infra-red spectra, are of particular interest because of the possibility that they may eventually be correlated with such molecular properties as bond orders and resonance energies.

Furthermore, one would expect the distortion of bond angles in an aromatic molecule to affect the state of hybridisation of the atoms involved; *e.g.*, it will be instructive to determine the degree of bending to which an exocyclic bond of a benzene ring may be subjected before the planarity of the six-membered ring itself is affected. Of particular interest also is the manner in which the effects of overcrowding in one part of a highly conjugated molecule may be transmitted to distant parts of the conjugated system.

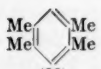
Such distortions of aromatic ring systems must lead to wider variations in bond lengths and electron-density distribution than have so far been found in " normal " molecules like naphthalene, anthracene, etc.; correlation of these variations with the chemical properties of the overcrowded compounds may possibly lead to a better understanding of the relation between structure and reactivity.

Finally, the static deformations of the aromatic system within an overcrowded molecule owing to intramolecular compression may be expected to serve as models for the dynamic distortions produced by the approach of a reagent molecule towards the normal aromatic system in the course of a chemical reaction. These distortions are not, of course, susceptible to direct observation; nevertheless, the mode of deformation of an aromatic system produced by the penetration of its van der Waals envelope, by an uncharged (free-radical) reagent in particular, and the structure of the activated complex formed by the coalescence of the two components may well become deducible by analogy with overcrowded structures.

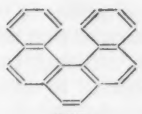
In our examination of the distortions produced in overcrowded aromatic compounds, we begin with certain molecules exhibiting close contact between benzene rings or their substituents. Four general types of such molecules will be considered. These are: *Group I: Substituted benzenes, e.g.*, *o*-dichlorobenzene (I), durene (II). *Group II: Aromatic polycyclics, e.g.*, 3 : 4-5 : 6-dibenzophenanthrene (III), tetrabenzonaphthalene (IV). *Group III:*

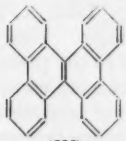


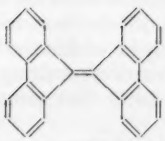
(I)

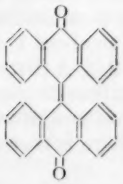


(II)

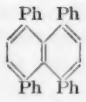

(III)


(IV)

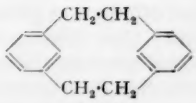

(V)



(VI)



(VII)



(VIII)

Tetraphenylethylenes bridged at all 2-positions, e.g., difluorenylidene (V), dianthronylidene (dianthrone) (VI). *Group IV: Molecules containing overcrowded phenyl rings, e.g.*, 1 : 4 : 5 : 8-tetraphenylnaphthalene (VII), di-*m*-xylylene (VIII). The following review of previous work conforms to the foregoing classification.

Group I.—In studies of hexachloro- and hexabromo-benzene by electron diffraction (Bastiansen and Hassel, *Acta Chem. Scand.*, 1947, **1**, 489) the exocyclic bonds of both molecules were found to be bent out of the planes of the benzene rings by about 12°. In the corresponding *o*-dihalogeno-derivatives the same authors found that the distances between the substituents were consistent with an 18° bending of the carbon–halogen bonds out of the planes of the rings but could also be accounted for by a smaller out-of-plane bending together with a slight in-plane bending towards the unsubstituted positions. Their findings for

1 : 2 : 3 : 5-tetrabromobenzene also fell into line, with an apparent 15° out-of-plane bending of the exocyclic bonds to the three overcrowded bromine atoms, again with the possibility that the actual bending was less than this, being supplemented by a slight displacement of the 1- and the 3-bromine atom away from the 2-substituent.

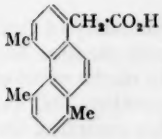
These electron-diffraction results appear to be contradicted, however, by an *X*-ray crystallographic structure analysis of hexachlorobenzene (Lonsdale, *Proc. Roy. Soc.*, 1931, *A*, **133**, 536). Although only one Fourier projection was obtained, down an axis roughly perpendicular to the molecular plane, this map is quite incompatible with the configuration reported by Bastiansen and Hassel (*loc. cit.*) for the molecules in the vapour. Lonsdale's co-ordinates for the chlorine atoms may be fitted, with a root-mean-square deviation of 0·013 Å, to a regular planar hexagon inclined at 23° to the plane of projection. Unless the structure she published is wrong by more than 0·1 Å *parallel to the plane of projection* it cannot be reconciled with an out-of-plane displacement of about 0·35 Å such as is implied by Bastiansen and Hassel's interpretation of their electron-diffraction data. It seems very unlikely that the molecules in the vapour could have the shape indicated by the electron-diffraction spectra and yet be compressed into a planar configuration by packing forces in the crystal. It is more probable that they are in fact planar, in the ground state, but that a strong correlation between the out-of-plane vibrations of the chlorine atoms, which are probably markedly anharmonic, accounts for the greater average separation between *ortho*-substituents observed in the vapour. The alternative explanation, that the ground-state configuration is non-planar and that the apparent planarity in the crystal is a statistical effect due to thermal oscillation between two mirror-image configurations, receives no support from the peak shapes in the published electron-density projection and seems inherently improbable. If any of these explanations is correct, however, it would indicate that there is a strong repulsion between neighbouring chlorine atoms which tends to stabilize the non-planar configuration. Similar considerations probably apply to hexabromobenzene, whose crystals are isomorphous with those of hexachlorobenzene (Plummer, *Phil. Mag.*, 1925, **50**, 1214).

Crystallographic structure analyses of hexamethylbenzene (Lonsdale, *Proc. Roy. Soc.*, 1929, *A*, **123**, 494; Brockway and Robertson, *J.*, 1939, 1324) and durene (Robertson, *Proc. Roy. Soc.*, 1933, *A*, **142**, 659) indicate that in each of these compounds the carbon atoms are all coplanar. Well-resolved projections of both structures show the molecules sufficiently inclined to the planes of projection so that an out-of-plane displacement of as little as 0·1 Å could scarcely escape detection, although the incompleteness of the Fourier series used in the durene analysis makes it difficult to estimate the true limits of error in this structure. The distance between the *ortho*-substituents is given as 2·9 Å in hexamethylbenzene and as 3·0 Å in durene, the greater separation in the latter arising apparently from a bending of the exocyclic carbon–carbon bonds towards the unsubstituted positions. The extent of this bending, originally reported as 3°, is reduced to about 1° if the distance from the centre of the molecule to the methyl carbons is taken as 2·92 Å (Brockway and Robertson, *loc. cit.*) instead of 2·88 Å as given originally. Such a small bending could easily lie within the limits of error; thus there seems to be no conclusive evidence of any deformation resulting from repulsion between the methyl groups although there is no reason to doubt that some such deformation does occur.

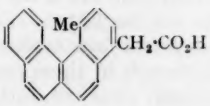
Group II.—To this category belongs the classical work of Newman and his school on the optical activity of 4 : 5-dimethylphenanthrenes (IX) (Newman and Hussey, *J. Amer. Chem. Soc.*, 1947, **69**, 3023) and 5-methyl-3 : 4-benzophenanthrenes (X) (Newman and Wheatley, *ibid.*, 1948, **70**, 1913). However, while the existence of optical enantiomorphs demonstrates the non-planarity of these molecules, the type of distortion, whether of the substituents out of the plane of the nucleus or of the ring system itself, cannot be deduced from the optical evidence.

The situation is similar with regard to 4 : 5-dimethylphenazone, whose non-planarity has recently been proved by the optical resolution of (XI) (Theilacker and Baxmann, *Annalen*, 1953, **581**, 117). That 3 : 4-5 : 6-dibenzophenanthrene is also non-planar follows from the partial optical resolution of (XII) (Bell and Waring, *loc. cit.*). A direct structure analysis of the hydrocarbon has been carried out by McIntosh, Robertson, and Vand (*Nature*, 1952, **169**, 322), who report that " the steric effect has resulted almost entirely in

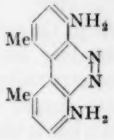
distortion from a planar arrangement with little change in the hexagonal form of the benzene rings." The distance between the overcrowded atoms is given as approximately 3·0 Å, but the precise nature of the distortions is unknown.



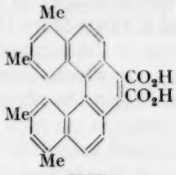
(IX)



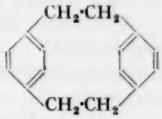
(X)



(XI)



(XII)



(XIII)

In octamethylnaphthalene the 1- and 8-methyl carbon atoms would approach to within 2·4 Å if the molecule were planar and regular. A crystallographic analysis (Donaldson and Robertson, *J.*, 1953, 17) has shown that they are displaced by 0·73 Å from the mean molecular plane and that the 2-methyl carbons also deviate from the mean plane, their displacement being estimated as 0·25—0·40 Å. There is, in addition, some indication that the naphthalene nucleus itself may be non-planar, but this is much less definitely established than the displacements of the substituents. These displacements, which must be assumed to alternate in direction around the nucleus, cause the approach distances between neighbouring methyl carbons all to be greater than 2·9 Å. That the 2-methyl groups are displaced from the mean molecular plane although their approach distances are at least as great as those between *ortho*-substituents in hexamethylbenzene, which is planar, may be due largely to the fact that the overcrowding of the 1- and 8-methyl groups destroys the planarity of the molecule and causes the repulsion between the 1- and 2-methyl groups, even at a separation of about 3·0 Å, to have an appreciable component normal to the mean plane such as is lacking in hexamethylbenzene. We conclude tentatively that repulsion between methyl groups is considerable at distances up to 3·0 Å at least, although in molecules of high symmetry it may not result in any observable deformation.

Group III.—The only representative of this group whose structure has been reported is difluorenylidene (Fenimore, *Acta Cryst.*, 1948, **1**, 295). An incomplete three-dimensional analysis has yielded a centrosymmetric model described as approximately planar; the overcrowded atoms are said to be 2·5 Å apart. It is doubtful whether the structure has been refined sufficiently to permit significant conclusions with regard to the molecular dimensions. The high discrepancy factors, $R(hk0) = 0{\cdot}31$ and $R(hkl) = 0{\cdot}36$, indicate that the structural details have not been fully established. The approach distance of 2·5 Å, which is considerably shorter than any observed in similar overcrowded structures, must therefore be regarded as questionable.

Group IV.—In di-*p*-xylylene (XIII) (Brown, *J.*, 1953, 3265) analysis from three-dimensional data shows that the separation between the unsubstituted carbon atoms of the two rings is 3·09 Å, and the substituted carbons are 2·83 Å apart. Thus the substituted atoms in each ring are displaced by 0·13 Å from the plane of the four unsubstituted carbons, giving the rings a folded, or "boat" shape. The bond angles at the aliphatic carbon atoms are 114° 37′. In addition, the three bonds to each substituted carbon atom are not coplanar, the exocyclic bond making an angle of about 13½° with the plane of the two aromatic bonds. Nevertheless, all benzene bond lengths are said to be 1·39 or 1·40 Å, and hence there is no evidence that the non-planarity of the rings involves any loss of resonance.

The same effect occurs in centrosymmetric di-*m*-xylylene also the subject of a three-dimensional analysis (Brown, *J.*, 1953, 3278), which reveals a similar bending of the benzene rings due to repulsion between the two carbon atoms, one in each ring, *ortho* to the substituted positions. These carbon atoms are only 2·69 Å apart, and each is displaced by 0·143 Å from the mean plane of ring atoms 2, 3, 5, and 6 (the overcrowded atom being numbered 1). Atom 4 is also displaced from this plane, by 0·042 Å, so that the deformation of the ring may be regarded as consisting in part of a folding about the diagonal 1—4. If chemically-equivalent bond lengths are averaged, those of all the benzene bonds are found

to lie between 1·38 and 1·39 Å. It is likely that correction for overlap of adjacent peaks and series-termination would result in a slightly higher estimate for these bond lengths, but the very close equality of all aromatic bonds seems to be established. The bond angles within the ring, when averaged in accordance with an assumed molecular mirror plane through atoms 1 and 4, range from 117° to 122°.

A common feature of the compounds in Groups I, II, and III is the planarity of their conventional models in which overcrowding forces are neglected. Consequently, any deviation from planarity in the observed structures is *prima facie* evidence of the effect of intramolecular compression on molecular shape. Although in these compounds and the two in Group IV discussed above the situation is thus fairly clear cut, further complications are presented by such borderline structures as diphenyl and *trans*-stilbene. Here the chemical forces tending to maintain a planar configuration appear to be of the same order of magnitude as the lattice forces responsible for crystal formation. Accordingly, the latter cannot be ignored in any discussion of the equilibrium between intramolecular compression and chemical bonding forces. On the assumption that coplanarity of the two rings in diphenyl leads to maximum resonance and hence to the lowest molecular-energy state, one arrives at a model in which the distance between carbon atoms 1 and 1′ is about 2·9 Å. In fact, while diphenyl in the solid state is centrosymmetric and thus planar (*e.g.*, Hengstenberg and Mark, *Z. Krist.*, 1929, **70**, 283), electron diffraction by the vapour (Bastiansen, *Acta Chem. Scand.*, 1949, **3**, 408) indicates that the two rings are inclined to one another at an angle of about 45°. The obscure situation discussed above with regard to hexachlorobenzene demands caution in interpretation of any apparent discrepancy between crystallographic and electron-diffraction data as implying a real difference between the molecular configurations in the solid and in the gaseous phase. Nevertheless, it seems reasonable to assume, in accordance with Bastiansen's suggestion (*loc. cit.*), that the energy of repulsion between the overcrowded atoms in diphenyl exceeds the gain in resonance energy achieved by the planar configuration but that this difference is insufficient, in the solid state, to offset the gain in lattice energy that results from the easier packing of the planar molecules.

In *trans*-stilbene, as in diphenyl, the structure with maximum resonance energy is, presumably, the planar configuration, in which the separation between carbon atoms 1 and α' would be under 2·9 Å if all bond angles were 120°. This overcrowding could be relieved either by a twist of the benzene rings out of the plane of the central ethylenic system or by an increase of the C–C=C angle. A crystallographic analysis (Robertson and Woodward, *Proc. Roy. Soc.*, 1937, *A*, **162**, 568), based on only one projection, reveals two types of stilbene molecule in the crystal. In one, the angle of twist is given as 10·4° and the C–C=C angle as 128°, while for the other the corresponding values are 2·8° and 133°. The two mechanisms for the relief of overcrowding thus appear to be complementary, each predominating in one of the two molecular species. The difference between the two molecules, if real, must be attributed to their different environments in the crystal.

Clearly, compounds in which steric repulsion leads to rotation about a bond of intermediate bond order present greater difficulties in interpretation than compounds whose conventional bond structures are unambiguously planar. The work to be described in this series of papers has therefore been confined to molecules of the latter type.

The evidence summarised above indicates that repulsion between non-bonded atoms may result in a wide variety of observable deviations from the conventional molecular configurations. Such deviations are often expressed in non-planarity of aromatic systems, involving distortions in the planar valency distribution of the trigonal carbon atoms, as well as abnormal bond angles at both aromatic and aliphatic carbon atoms. One useful generalisation that seems to be warranted by these data is that repulsion between non-bonded carbon atoms at a distance of 3·0 Å or less is sufficient, in many compounds, to produce appreciable deformations. But even this conclusion, while it may serve at this stage to provide an empirical criterion for overcrowding between carbon atoms, must be regarded as questionable in view of the structure reported for difluorenylidene and also in view of the as yet unexplained intermolecular approach distance of 2·58 Å found in crystals of triphenylene (Klug, *Acta Cryst.*, 1950, **3**, 165).

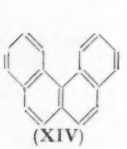
The first step in the present experimental study of the problems outlined here was a

crystallographic survey of several aromatic structures in which the forces due to overcrowding may be expected to lead to conspicuous deviations from the hypothetical planar configuration. Because of the complexity of many of these molecules and the uncertainty as to their shapes it was considered advisable to begin this investigation with a preliminary

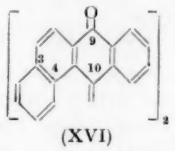
Compound	*a* (Å)	*b* (Å)	*c* (Å)	*β*	Space-group	*d* calc.	*d* exp.	*n*	Mol. sym.	
3 : 4-Benzophenanthrene (XIV)	14·69	14·19	5·76	—	$P2_12_12_1$	1·261	1·265	4	—	See Part III
5 : 4′-Dimethyl-3 : 4-benzophenanthrene (XV)	15·53	12·44	7·25	—	*Pbna*	1·214	—	4	2	
3 : 4-5 : 6-Dibenzophenanthrene (III)										
α-form	25·96	8·88	19·46	104°	*A*2/*a*	1·27	1·27	12	2	By sublimation (cf. McIntosh, Robertson, and Vand, *Nature*, 1952, **169**, 322)
β-form	17·46	14·24	5·83	94°	$P2_1/a$	1·27	1·26	4	—	From acetic acid
9 : 10-Dihydro-3 : 4-5 : 6-dibenzophenanthrene	20·0	20·0	7·43	—	$P4_32_1$	1·26	1·271	8	—	
Tetrabenzonaphthalene (IV)	20·45	7·74	12·18	119° 33′	$P2_1/a$	1·275	1·292	4	—	See Part IV
Dianthronylidene (VI)	10·20	8·45	12·67	119° 48′	$P2_1/c$	1·345	1·35	2	$\bar{1}$	See Part II
1 : 1′-Dibromodianthronylidene	10·31	27·76	7·66	102° 30′	$P2_1/n$	1·675	1·695	4	—	
1 : 1′-Dimethyldianthronylidene	9·99	27·35	7·66	92° 22′	$P2_1/n$	1·307	1·320	4	—	
3 : 4-3′ : 4′-Dibenzodianthronylidene (XVI)	14·7	11·5	7·6	α = 101° β = 92° γ = 103°	*P*1 or $P\bar{1}$	1·326	1·33	2	—	
Dixanthylidene (XVII)										
α-form	15·19	6·26	18·93	93° 9′	*Aa* or *A*2/*a*	1·32	—	4	possibly $\bar{1}$ or 2	Blue plates, obtained only once. Decompose to yellow powder
β-form	14·87	12·90	9·41	95° 15′	*Cc* or *C*2/*c*	1·314	1·326	4	$\bar{1}$ or 2	Wilson test indicates *C*2/*c*. Both blue and yellow needles found
9-Xanthylidene-anthrone (XVIII)	25·02	8·75	12·63	98° 30′	$P2_1/a$	1·35	1·35	6	($\bar{1}$) 2	Molecules have statistical centres of symmetry
10 : 10′-Dimethyldiacridylidene (XIX)	13·21	12·40	12·55	91° 30′	$P2_1/c$	1·27	1·31	4	—	
Dithioxanthylidene (as XVII)	5·73	17·98	18·11	—	*Pbc* or *Pbcm*	1·395	1·390	4	$\bar{1}$ or 2	Wilson test indicates *Pbcm*
Difluorenylidene (V)										
α-form	17·2	36·9	8·23	—	*Pcan*	1·28	1·26	12	$\bar{1}$ (or 2)	Cf. Fenimore, *Acta Cryst.*, 1948, **1**, 295
β-form	19·43	9·02	9·75	—	$P2_12_12_1$	1·276	1·283	4	—	Cf. Groth, Vol. V, 431
Bis-1 : 2-3 : 4-dibenzofluorenylidene (XX)	47·0	21·9	7·45	—	*Pnca*	1·37	1·38	12	$\bar{1}$ or 2	
Bisdibenzosuberenylidene (XXI)	11·3	16·6	11·6	107° 30′	$P2_1/n$	1·22	1·25	4	—	

study of as many compounds of this type as were available to us in the hope that some information regarding molecular shape could be derived from the cell dimensions and space-groups even before complete crystallographic analyses of the more promising structures were undertaken. The Table summarises the results of this survey. All cell dimensions were determined from Weissenberg photographs with nickel-filtered copper radiation and are accurate to 1% or better.

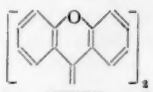
Little information on molecular shape of the compounds in Group II can be deduced from the preliminary data. Comparison of the series 3 : 4-benzophenanthrene, 5 : 4′-dimethyl-3 : 4-benzophenanthrene, β-3 : 4-5 : 6-dibenzophenanthrene, suggests that the lattice arrangements of these hydrocarbons, and hence their molecular shapes, must be closely related, a conclusion that is borne out by the correspondence in relative intensities of the low-order *hk*0 reflections of the three crystal structures. Since both 5 : 4′-dimethyl-3 : 4-benzophenanthrene and 3 : 4-5 : 6-dibenzophenanthrene (in the α-modification) crystallise with exact molecular twofold axes of symmetry, one may assume that 3 : 4-benzophenanthrene at least approximates to twofold symmetry.


(XIV)

(XV)

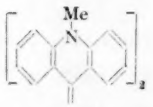


(XVI)

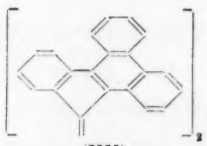


(XVII)

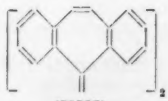
(XVIII)



(XIX)



(XX)



(XXI)

In the dianthronylidene series (Group III) a number of compounds crystallise with centres of symmetry. Thus, dianthronylidene occurs in space-group $P2_1/c$ with two molecules in the unit cell; it follows unambiguously that it possesses a molecular centre of symmetry. In β-dixanthylidene the systematic absences alone do not allow of a choice between space-groups Cc and $C2/c$; however, the Wilson test (*Acta Cryst.*, 1949, **2**, 318) shows that the crystals are centric and that their space-group must therefore be $C2/c$ (Harnik, Herbstein, and Schmidt, *loc. cit.*). As there are four molecules in the unit cell they must have either a molecular centre or a twofold axis of symmetry. The latter being unlikely for reasons of space requirement, one may conclude that dixanthylidene, like dianthronylidene, is centrosymmetric. The asymmetrical xanthylideneanthrone crystallised in space-group $P2_1/a$ with six molecules in the cell; two molecules therefore possess pseudo-centres of symmetry, which can only be explained by the random packing of their long axes in the crystal lattice. Of the substituted dianthronylidenes only the isomorphous pair, 1 : 1′-dimethyl- and 1 : 1′-dibromo-dianthronylidene, have been studied. Here the crystallographic situation imposes no symmetry requirements on the molecules; nevertheless, the similarities in cell dimensions with the parent compound (after allowance for the interchange of the *b* and *c* axes and for the larger number of molecules per cell in the substituted derivatives) suggest that the shapes and space requirements of these compounds are essentially similar.

A second modification of difluorenylidene has the space group $P2_12_12_1$. Since centrosymmetric molecules rarely crystallise in non-centric space groups, it is possible that the molecule here, unlike the modification analysed by Fenimore (*loc. cit.*), has either no symmetry or else a (non-crystallographic) twofold axis.

These conclusions with regard to molecular symmetry in the various classes of compounds provide no detailed information on the nature or extent of the deformations present in these molecules, which can be determined only by complete structure analyses; these will accordingly be the subjects of later papers in this series.

WEIZMANN INSTITUTE OF SCIENCE,
REHOVOTH, ISRAEL.

[*Received, January 11th*, 1954.]

The Structure of Overcrowded Aromatic Compounds. Part II. The Crystal Structure of Dianthronylidene.*

By E. HARNIK and G. M. J. SCHMIDT.

[Reprint Order No. 5060.]

The crystal structure of dianthronylidene (dianthrone) has been analysed by two-dimensional Fourier methods. The molecular centre being fixed by space-group symmetry, the molecular orientation and the signs of approximately half the *h0l* structure factors were determined by the method of the molecular Fourier transform, calculated for a planar molecular model. The three zonal projections were refined by successive $F_o - F_c$ syntheses to R factors of 0·19, 0·19, and 0·20 in the *h0l*, *hk*0, and 0*kl* zones.

A molecular model has been obtained, approximating to symmetry 2/*m*, in which a centre-to-centre distance of 2·90 Å between the overcrowded carbon atoms 4 and 4′, and 8 and 8′, is achieved by a 40° rotation of the benzene rings out of the plane of the central ethylenic system; this rotation is accompanied by compression of the $\begin{matrix}C\\C\end{matrix}\!>\!C=$ angle to 113° and by deflection of the exocyclic bonds to the carbonyl carbon by 8° out of the planes of their respective benzene rings. The observed bond lengths and angles indicate that the molecule consists of an isolated ethylenic group (1·31 Å) attached by single bonds (1·53 Å) to normal benzene rings, which in turn are linked to a carbonyl group (1·20 Å) by single bonds (1·52 Å).

The absence of abnormally-short intermolecular contact distances in the crystal lattice indicates that the present molecular model may be identified with the ground state of dianthronylidene.

THE crystal structure of dianthronylidene (Fig. 1) † was determined in connection with a general investigation outlined in Part I.* The immediate purpose of this study was to determine the molecular shape of dianthronylidene with particular reference to the distance between the carbon atoms 4 and 4′ and 8 and 8′. The present paper reports the results of a structure analysis by two-dimensional Fourier methods and discusses the mechanism of relief of overcrowding.

Table 1 lists the crystallographic constants of dianthronylidene and of those of its derivatives that were available at the start of this work. For the purpose of an X-ray crystallo-

TABLE 1. *Crystallographic constants of dianthronylidene and some derivatives.*

	a	*b*	*c*	*β*	Space-group	*d* calc.	*d* exp.	*n*	Mol. sym.
Dianthronylidene	10·20	8·45	12·67	119° 48′	$P2_1/c$	1·345	1·35	2	Ī
4 : 4′-Dibromo-	10·31	27·76	7·66	102° 30′	$P2_1/n$	1·675	1·695	4	—
4 : 4′-Dimethyl-	9·99	27·35	7·66	92° 22′	$P2_1/n$	1·307	1·320	4	—
3 : 4-3′ : 4′-Dibenzo-	14·7	11·5	7·6	α, 103° β, 92° γ, 101°	$P1$ or $P\bar{1}$	1·326	1·33	2	—

graphic analysis, only dianthronylidene itself and the isomorphous pair, 4 : 4′-dibromo- and 4 : 4′-dimethyl-dianthronylidene, seemed promising, the other derivative being too complex. Since so far we have not been able to grow entirely satisfactory crystals of the dibromo-compound, work was begun on dianthronylidene. From the lattice parameters of the crystals and their density, measured by flotation in a solution of potassium mercuri-iodide, it follows that there are two molecules in the unit cell. Hence, each molecule must possess a centre of symmetry, which may be placed at the points (000) and $(0\frac{1}{2}\frac{1}{2})$, and the problem of the structure analysis reduces to the determination of the (*xyz*) co-ordinates of 15 atoms, the hydrogen atoms being neglected.

* Part I, preceding paper.

† In this paper the numbers used in references to the carbon atoms are as shown in Fig. 1 and not those strictly related to the name dianthronylidene.

Experience gained with the molecular Fourier transform method in the early stages of structure analysis suggested the use of the method in this instance. Apart from the limitations discussed below, we may say that the structure was solved by means of the Fourier transform. The simple form, as first applied to structure analysis by Knott (*Proc. Phys. Soc.*, 1940, **52**, 229) and later elaborated by Klug (*Acta Cryst.*, 1950, **3**, 176) (see also Herbstein and Schmidt, *Bull. Res. Council, Israel*, 1951, **1**, 123), strictly applies only to planar molecules, for which the Fourier transform is a function of the co-ordinates in the molecular plane only and can therefore be readily calculated as a two-dimensional series. In general, it consists of a real and an imaginary part, the latter vanishing for centrosymmetric molecules. Although dianthronylidene is in fact centrosymmetric, it cannot *a priori* be assumed planar, and hence the simple form of the Fourier transform method may not be applicable. Nevertheless, one could envisage the possibility that, calculated on the simplifying assumption of a planar molecule, it might give a sufficiently good first approximation, at least in one zone; the necessary condition would be that the projected view of the real molecule should not deviate markedly from the projection of the fully planar model. That this condition would be fulfilled for the *h*0*l* zone was indicated by the relatively short *b* axis in dianthronylidene, and the still shorter *c* axis in 4 : 4′-dibromodianthronylidene; it appeared that the molecules in each compound were packed in a two-layer structure along the short axis, rather than at the steep angle to this axis required by the estimated molecular dimensions.

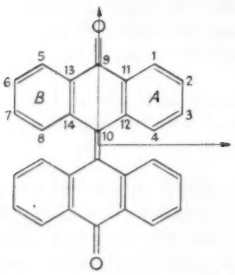


FIG. 1. *The planar model of the dianthronylidene molecule, showing the molecular axes and the nomenclature of the atoms used in this paper.*

The molecular Fourier transform of dianthronylidene was therefore calculated on the assumption of a planar model containing regular benzene rings of side 1·40 Å; in order to maintain periodicity, and hence to facilitate computation, the central C=C bond and the C=O bond were also assigned lengths of 1·40 Å. The contributions of the oxygen and carbon atoms were weighted in the ratio 8 : 6.

The map of the Fourier transform was compared with the plot of the weighted reciprocal lattice in the usual way, and the molecular axes were adjusted with respect to the reciprocal axes until fair agreement was obtained between observed and calculated structure factors. It was found that *three* orientations, at 120° to one another, gave roughly equal agreement for structure factors up to 2 sin $\theta = 1{\cdot}5$. The explanation for the indeterminacy in the Fourier transform method lies primarily in the approximate sixfold symmetry in the distribution of the areas of heavy scattering in the Fourier transform of dianthronylidene and in the uncertainty of the finer detail outside these areas. The three Fourier projections on to (010), each calculated from about 45 terms, including most of the strong reflections,

TABLE 2.—*Values of the agreement factor R for* F(h0l) *up to* 2 sin $\theta = 1{\cdot}0$, *showing the progress of refinement of the atomic co-ordinates derived from* ρ_I, ρ_{II}, *and* ρ_{III}.

Orientn.	Refinement no.			Orientn.	Refinement no.			Orientn.	Refinement no.		
no.	1	2	3	no.	1	2	3	no.	1	2	3
I	46	42	40	II	45	48	—	III	40	37	33

to which phase angles could be assigned from the corresponding Fourier transform orientation, were refined successively until a selection among them could be made on the basis of the relative improvement of the agreement factors. Table 2 shows the *R* factors, for F(*h*0*l*) up to 2 sin $\theta = 1{\cdot}0$, for the initial structure and after one and two stages of refinement. Orientation III was found to improve faster than I or II and was therefore chosen

as likely to lead to the correct structure. Further refinement was made by the use of the $F_O - F_C$ synthesis. The final Fourier projection on to (010) is shown in Fig. 2; it is clear at this stage that the molecule is not planar.

The projected view of the molecule is consistent with several more or less plausible models; structure factors F(*hk*0) and F(0*kl*) were computed for these possibilities up to $2 \sin \theta = 0{\cdot}7$, and that model was chosen for which the *R* factor was lowest. Refinement of both zones was again carried out by the $F_O - F_C$ method; owing to the very heavy overlap, which affects different groups of atoms in the two projections, the two zones were refined alternately, with the *y* co-ordinates from one zone as the starting point in the second, and *vice versa*. The final *y* co-ordinates are the result of the minimisation technique

FIG. 2. *The electron-density projection on* (010). *The contours are drawn at intervals of* 1 e.Å^{-2}; *the lowest contour is the one-electron line.*

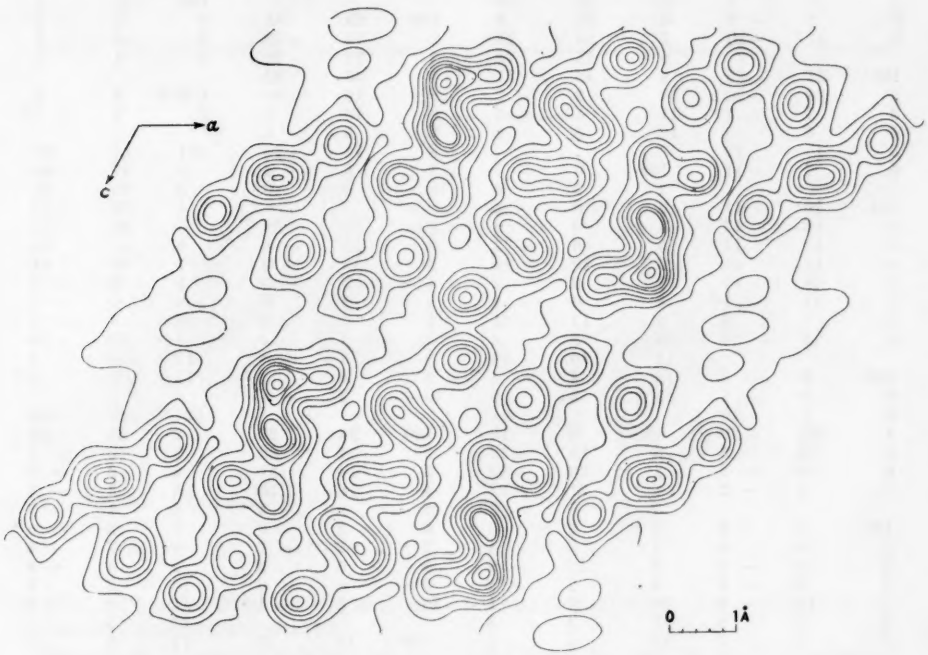


TABLE 3.—*Experimentally-measured atomic co-ordinates* (*in* Å).

Atom *	*x*	*y*	*z*	Atom *	*x*	*y*	*z*	Atom *	*x*	*y*	*z*
1	4·28	1·28	3·92	6	−1·83	0·34	3·53	11	2·81	0·72	3·09
2	4·86	2·07	3·22	7	−2·73	0·64	1·94	12	1·89	0·92	1·51
3	3·96	2·33	1·61	8	−2·08	0·57	1·05	13	0·40	0·00	3·21
4	2·38	1·77	0·75	9	2·17	−0·06	3·93	14	−0·53	0·28	1·62
5	−0·22	0·06	4·19	10	0·27	0·33	0·65	O	2·95	−0·44	5·23

* See footnote, p. 3295.

without extraneous assumptions on molecular dimensions. Although the *x* and *z* co-ordinates from the *h*0*l* zones were used in the calculation of the first set of *hk*0 and 0*kl* structure factors, these co-ordinates were changed during the course of refinement of the two projections. The values resulting from this refinement were averaged with those originally obtained from the *h*0*l* zone to give the final *x* and *z* co-ordinates listed in Table 3; the observed and calculated structure factors are compared in Table 4. Final *R* factors

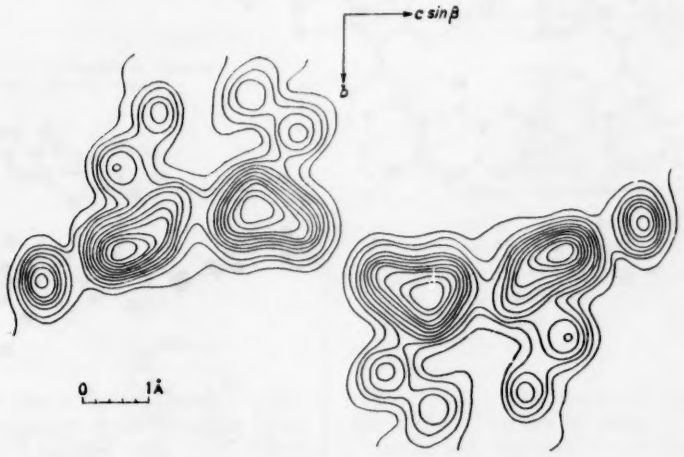
TABLE 4.—*List of observed and calculated structure factors.*

hkl	F_o	F_c	*hkl*	F_o	F_c	*hkl*	F_o	F_c	*hkl*	F_o	F_c
002	44	−59	$30\bar{4}$	11	− 8	060	6	− 6	470	0	− 3
4	16	−13	4	4	1*	8	5	1*	5	0	1
6	31	−26	5	6	8	10	2	− 1	6	3	0*
8	0	4	6	11	16				7	2	6
10	6	− 9	7	8	− 8	110	31	−28	8	0	1
12	5	4	8	0	− 2	2	24	−23			
14	6	− 4	9	8	8	3	20	−17	180	0	1
			10	5	4	4	25	21	2	9	13
100	34	40	11	4	− 5	5	9	− 8	3	6	− 2*
2	32	−28				6	2	− 4	4	0	− 1
3	11	8	$10\bar{6}$	3	2	7	3	2	5	6	5
4	54	55	2	24	33	8	0	1	6	4	4
5	36	29	3	4	− 3	9	4	− 3	7	0	− 4
6	5	− 3	4	13	− 9	10	2	0*			
7	3	2	5	28	29				190	0	3
8	7	− 6	6	10	− 9	120	69	85	2	0	4
9	11	−10	7	10	12	2	14	−13	3	5	− 3
			8	12	12	3	32	26	4	4	3
102	27	29	9	18	17	4	36	33			
2	24	−20	10	3	− 2	5	10	10	1,10,0	4	6
3	7	− 7	11	4	− 5	6	10	9	2	8	− 3*
4	5	3	12	5	8	7	5	5			
5	12	13				8	11	−10	011	17	22
6	7	−11	$10\bar{8}$	0	− 1	9	6	− 5	2	37	−48
			2	5	6	10	0	0	3	22	26
104	10	−11	3	0	6				4	28	−28
2	15	17	4	0	0	130	38	36	5	25	−32
3	12	−11	5	6	− 7	2	10	− 5	6	14	14
4	15	14	6	10	10	3	10	− 8	7	16	14
5	19	−17	7	0	2	4	3	− 5	8	2	− 2
6	11	− 1*	8	0	− 1	5	9	9	9	0	− 2
7	7	6	9	17	−21	6	0	2	10	0	− 2
8	3	4	10	3	4	7	0	− 1	11	13	−10
			11	10	14	8	8	− 4	12	5	4
106	0	− 1	12	4	− 4	9	4	1*	13	1	0*
2	0	− 1	13	3	− 6	10	3	− 4			
3	4	10							021	42	−55
4	23	−20	$10,\bar{1}0$	8	10	140	24	20	2	22	−21
5	3	− 2	2	13	−12	2	24	23	3	0	− 1
6	0	− 2	3	20	−20	3	14	11	4	8	− 6
7	4	− 2	4	31	−33	4	16	16	5	3	− 3
			5	5	− 3	5	8	8	6	4	− 3
108	5	− 3	6	0	0	6	6	6	7	2	0*
2	8	8	7	0	− 4	7	8	− 7	8	7	− 4
3	0	− 1	8	10	− 9	8	5	3	9	4	− 4
4	8	− 6	9	7	− 8	9	0	0	10	0	1
5	10	− 9	10	0	1	10	3	− 1*	11	0	2
6	0	0	11	3	5				12	5	5
7	2	− 3	12	5	5	150	18	23	13	2	2
						2	4	7			
10,10	18	−16	$10,\bar{1}2$	8	− 8	3	8	− 9	031	10	− 4*
2	5	− 4	2	3	− 2	4	0	− 3	2	31	−30
3	0	0	3	8	5	5	0	2	3	10	8
4	0	0	4	18	19	6	0	1	4	16	−13
5	5	6	5	14	−13	7	0	2	5	7	− 7
			6	4	− 4	8	5	5	6	10	9
10,12	5	4	7	5	7	9	8	11	7	10	8
2	5	− 2	8	3	2				8	5	3
			9	3	3	160	14	16	9	0	1
$10\bar{2}$	11	−12				2	17	20	10	0	2
2	16	−12	$10,\bar{1}4$	5	− 5	3	6	7	11	6	− 4
3	32	33	2	4	− 4	4	3	− 3	12	2	1
4	25	−26	3	4	3	5	11	10	13	3	− 3
5	22	−22	4	5	− 4	6	0	1			
6	16	15				7	0	− 1	041	24	−23
7	4	− 1*	$60,\bar{1}6$	5	− 7	8	2	− 3	2	14	−14
8	3	4	7	7	− 8	9	5	6	3	4	0*
9	11	15	8	3	− 4				4	10	8
						170	11	14	5	4	5
$10\bar{4}$	0	1	020	63	80	2	3	4	6	4	− 6
2	10	15	4	35	41	3	0	− 3	7	8	7

TABLE 4. (*Continued.*)

hkl	F_o	F_c	*hkl*	F_o	F_c	*hkl*	F_o	F_c	*hkl*	F_o	F_c
048	4	1 *	059	6	− 3	071	10	− 8	086	3	4
9	11	−11	10	4	6	2	0	− 2	7	4	− 3
10	8	− 6	11	2	− 2	3	9	8	8	2	4
11	0	1	12	3	− 1	4	10	− 9	9	2	− 1
12	2	2				5	10	− 8			
13	2	3	061	4	− 3	6	0	− 1	091	0	− 1
			2	7	− 6	7	6	4	2	0	3
			3	4	1 *	8	4	− 1 *	3	5	3
051	12	− 9	4	6	5	9	6	8	4	3	− 3
2	28	−30	5	9	− 9	10	4	4	5	2	− 2
3	23	25	6	12	12				6	2	3
4	10	−11	7	6	− 5	081	0	− 2			
5	5	− 5	8	11	− 9	2	10	−10	0,10,1	0	1
6	0	2	9	4	− 3	3	2	1	2	2	− 2
7	0	− 4	10	3	4	4	4	4	3	2	− 1
8	0	− 1	11	6	5	5	4	4	4	2	0 *

FIG. 3. *The electron-density projection down* [100]. *Contours below the three-electron line have been omitted.*



are 0·19, 0·19, and 0·20 in the *h*0*l*, *hk*0, and 0*kl* zones respectively. Fig. 3 shows the electron-density projection down [100].

Because of the considerable overlap in all three zones, the error in the final atomic co-ordinates is probably not less than 0·02 Å in x and z, though it may be somewhat smaller for the well-resolved atoms, and 0·05 Å in y. One can form an estimate of the former figure from the results of the $F_o - F_c$ syntheses in the *hk*0 and 0*kl* zones, for which the final co-ordinates differ by a maximum of 0·05 Å and a mean of 0·03 Å from those of the *h*0*l* zone. A second estimate can be based on the internal consistency of the molecular dimensions. Comparison of chemically-equivalent bond lengths (Fig. 7) shows an average deviation of 0·02 Å, with a maximum deviation of 0·06 Å, from the mean. A similar analysis of equivalent bond angles shows an average deviation of 1° and a maximum deviation of 3° from the mean. Within the estimated limits of error, the molecule has the chemically-reasonable symmetry 2/*m*.

The following discussion indicates that the final atomic co-ordinates, derived by the minimisation procedure of the $F_o - F_c$ synthesis, imply certain deviations from standard bond angles; some of these distortions are outside the limits of experimental error and are therefore real, while others can be removed by small shifts of atomic co-ordinates which lie within these limits.

The length of the central double bond of the ethylenic system is 1·31 Å. The lateral

bonds 10—12 and 10—14 are 1·54 and 1·52 Å long and enclose an angle of 113°. The doubly-bonded atom 10 does not lie in the plane defined by atoms 12 and 14 and the centre of symmetry but is displaced from it by 0·07 Å. This deviation from planarity is believed to lie within the experimental error, since a shift of atom 10 into this plane affects mainly its y co-ordinate.

The benzene rings A and B are rotated by 40° out of the plane of the ethylenic group. Both rings are planar, their atoms deviating by a maximum of 0·04 Å from their best planes.

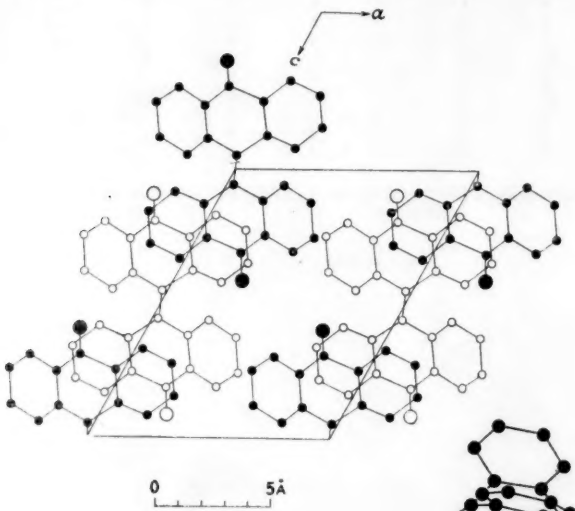


FIG. 4. *The projection of the unit-cell contents on* (010).

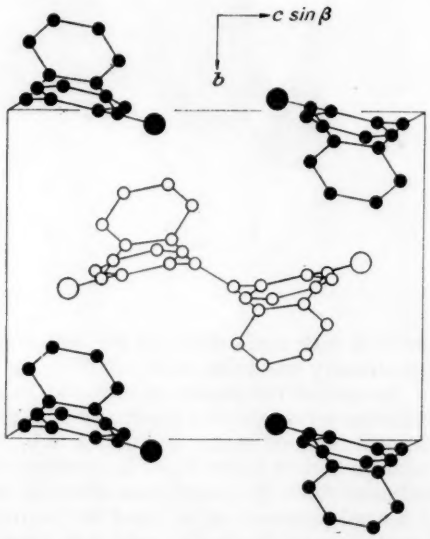


FIG. 5. *The projection of the unit-cell contents down* [100].

The bond lengths all lie within 0·06 Å of the mean value of 1·40 Å, and the bond angles within 3° of the mean value of 120°. The exocyclic bonds 10—12 and 10—14 to the central double bond both make angles of 2° with the planes of their respective benzene rings. This distortion is within the limit of experimental error; it depends chiefly upon the y co-ordinate of atom 10, in which a shift of 0·05 Å, in the same direction as that required to make the ethylenic system planar, would make both 2, 12, 10 and 6, 14, 10 collinear. The exocyclic bond 9—11 to the carbonyl group is inclined out of the plane of its benzene ring A so that it makes an angle of 7° with the prolongation of the ring diagonal 3—11, this angle lying in a plane perpendicular to the benzene ring. The corresponding angle between 9—13 and the plane of benzene ring B is 9°. These distortions are definitely beyond the limit of

experimental error since atom 9 would have to move by 0·18 Å in y in order to become collinear with 3—11 and 7—13. Furthermore, such a shift would stretch the exocyclic bonds 9—11 and 9—13 to 1·6 Å, make the oxygen atom lie 0·1 Å out of their plane, and compress the angle 11—9—13 to 106°.

The length of the double bond of the carbonyl group is 1·20 Å; the lateral bonds to the benzene rings are 1·52 and 1·51 Å long and enclose an angle of 116°. The four atoms of the carbonyl system are not strictly coplanar, as atom 9 is displaced by 0·07 Å and the oxygen atom by 0·06 Å from the most probable plane through 9, 11, 13 and the oxygen atom, but this apparent deviation from planarity is probably not significant as it involves primarily the y co-ordinates of the atoms.

The model of dianthronylidene deduced may be interpreted as consisting of a planar ethylenic group of central bond length 1·31 Å, attached to four phenyl groups by bonds which, owing to the angle of 40° between the planes of the ethylenic system and the benzene rings and the resulting absence of resonance interaction, have single-bond character (1·53 Å). The angle of twist is sufficient to produce a separation of 2·9 Å between carbon atoms 4 and 4′ and between carbon atoms 8 and 8′. With the lateral bonds of the ethylenic group making an angle of 113°, atoms 11 and 13 are 2·57 Å apart, permitting the insertion of the

FIG. 6. *A perspective view of the molecular model.*

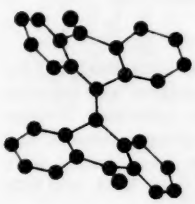
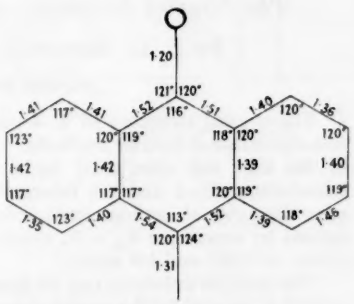


FIG. 7. *The dimensions of the experimental model.*



carbonyl bridge with C–C bond lengths of 1·52 Å and a C–C–C angle of 116°, but this involves distortion of the exocyclic bonds to the carbonyl carbon by about 8° out of the planes of their benzene rings. The structure of dianthronylidene thus resembles previously-analysed overcrowded structures in that the balance between intramolecular repulsion and forces due to bond distortion results in intramolecular approach distances of 2·9 Å, and that the distortions within the molecule are not localised but are distributed over several bonds.

The phenomena of thermochromy and photochromy (see, *e.g.*, Grubb and Kistiakowsky, *J. Amer. Chem. Soc.*, 1950, **72**, 419; Hirschberg and Fischer, *J.*, 1953, 629; Theilacker, Kortüm, and Friedheim, *Ber.*, 1950, **83**, 508) have been interpreted as evidence for the existence of more than one structure of dianthronylidene. In the absence of intermolecular carbon-to-carbon distances of less than 3·6 Å, it is unlikely that the structure determined here is to any appreciable extent affected by molecular packing in the crystal lattice. There is therefore no need to entertain the possibility of a change of configuration when the molecule passes from the crystalline to the dissolved state, and we assume that the ground state of dianthronylidene is correctly represented by the present model. We propose to discuss in a later paper possible structures for the excited state of dianthronylidene.

EXPERIMENTAL

Large crystals of dianthronylidene can be grown by slow cooling, over a week, of a solution in redistilled nitrobenzene. The crystals are monoclinic, yellow bipyramids elongated along [010], showing a variety of unidentified *hkl* faces. No previous data have been recorded; the entry in Groth's "Chemische Kristallographie," Leipzig, 1919, V, 440, under "Dianthron" refers to the dihydro-compound, dianthronyl.

The crystallographic constants were measured from zero-layer Weissenberg photographs about the three principal axes and corrected by extrapolation to $\theta = 90°$ (Buerger, "*X*-Ray Crystallography," John Wiley and Sons, 1942, Ch. 20). The space-group was identified as $P2_1/c$ from zero- and first-layer photographs about [010] and [100]. The zonal reflections were recorded on zero-layer Weissenberg photographs by the multiple-film technique, and their intensities estimated in the usual way. The *h0l* intensities were estimated independently by two observers; agreement between the two sets of intensities was sufficiently good to indicate an accuracy of 10% in mean F(*h0l*). The observed structure factors were placed on an approximately absolute scale by Wilson's method (*Nature*, **1942**, **150**, 152); later comparison with calculated structure factors showed that the scale had been underestimated by about 20%. The crystals reflect *X*-rays well; in the *h0l* zone out of the total number of reflections within the limiting sphere for Cu-$K\alpha$ radiation 81% were recorded.

Our thanks are due to Professor E. D. Bergmann and Dr. E. Loewenthal for supplying dianthronylidene and its derivatives.

THE LABORATORY OF *X*-RAY CRYSTALLOGRAPHY,
THE WEIZMANN INSTITUTE OF SCIENCE, REHOVOTH, ISRAEL. [*Received, January 11th*, 1954.]

The Structure of Overcrowded Aromatic Compounds. Part III. The Crystal Structure of* 3 : 4-*Benzophenanthrene.*

By F. H. HERBSTEIN and G. M. J. SCHMIDT.

[Reprint Order No. 5061.]

The crystal structure of 3 : 4-benzophenanthrene has been analysed by two-dimensional Fourier methods. The molecular orientation and position in the unit cell were fixed by a combination of the molecular Fourier transform method and the interpretation of non-space-group absences and near absences of certain zonal reflections. The atomic co-ordinates were refined by successive $F_o - F_c$ syntheses to *R* factors of 0·22, 0·23, and 0·26 in the *hk*0, 0*kl*, and *h*0*l* zones.

The final co-ordinates can be fitted, within a root-mean-square deviation of 0·03 Å, to a molecular model of symmetry 2, in which a separation of 3·0 Å between the centres of the overcrowded carbon atoms labelled 1 and 12 in Fig. 1 is achieved by distortion of the benzene rings. This model consists of two pairs of six-membered rings, related by a twofold axis, which are folded about their long diagonals through angles of 10° and 14°.

The distortions of the molecular skeleton have been related to the difference between the calculated and measured resonance energies and to the non-vanishing dipole moment; the nearly tetrahedral bond angles at four of the secondary carbon atoms to the close approach distance of 3·13 Å between two such atoms of neighbouring molecules, and to the preferential attack on these same atoms by electrophilic reagents.

THE analysis of the structure of 3 : 4-benzophenanthrene was undertaken in continuation of work outlined in Part I (*J.*, 1954, 3288). The distance of 2·4 Å between carbon atoms labelled 1 and 12 in Fig. 1 † in a conventional model of the molecule is shorter than the approach distances found in any of the overcrowded molecules discussed in Part I, and one may therefore expect the benzophenanthrene ring system to be distorted in order to achieve relief from overcrowding. To investigate quantitatively any such deformation we have determined the structure of 3 : 4-benzophenanthrene by *X*-ray crystallography, and now report the results of an analysis by two-dimensional Fourier methods.

A preliminary crystallographic investigation has been reported by Iball (*Z. Krist.*, 1938, **99**, *A*, 230), from which we cite the following data: $a = 14{\cdot}60$, $b = 14{\cdot}00$, $c = 5{\cdot}76$ Å;

* Part II, preceding paper.

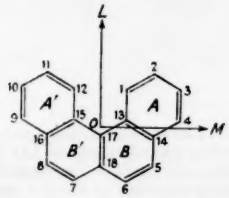
† In this paper the numbers used in references to the carbon atoms are those shown in Fig. 1 and not those strictly related to the name 3 : 4-benzophenanthrene.

d (found) 1·265, d (calc.) 1·278; $n = 4$. Absences: $h0l$ absent for $h + l$ odd, $0k0$ absent for k odd. Possible space-groups: $P2_12_12_1$, Pmn, $Pmnm$, with Pmn favoured on evidence referred to below.

The cell dimensions and space-group were now determined from zero- and first-layer Weissenberg photographs about the three principal axes. The lattice constants were corrected by extrapolation to $\theta = 90°$ (Buerger, "*X*-Ray Crystallography," J. Wiley and Sons, New York, 1942, Ch. 20) and are accurate to 0·1%: $a = 14·69$, $b = 14·19$, $c = 5·76$ Å; d (calc.) $= 1·261$. Absences: $h00$ absent for h odd, $0k0$ absent for k odd, $00l$ absent for l odd. Space-group: $P2_12_12_1$.

The two sets of lattice parameters are in good agreement. Our Weissenberg photographs show that the $h0l$ reflections with $h + l$ odd are weak but not systematically absent. Thus the extinctions referred to by Iball as systematic are in fact pseudo-absences; the space-group is therefore unequivocally determined as $P2_12_12_1$. The significance of these pseudo-extinctions for the molecular shape and arrangement is discussed in detail below.

FIG. 1. *The planar model of the* 3 : 4-*benzophenanthrene molecule, showing the molecular axes and the nomenclature of atoms and rings used in this paper.*



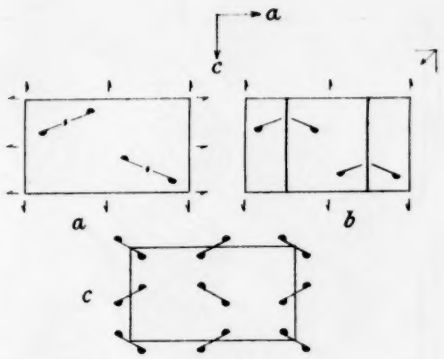


FIG. 2. *The* (010) *projections of the space-groups* (a) $P2_12_12_1$ *and* (b) $Pmn2_1$. *Possible molecular arrangements in* $P2_12_12_1$ *with the additional symmetry implied by the absences of* $h0l$ *spectra with* $h + l$ *odd are shown in* c *and* d.

In common with other workers, we prefer, for space-group $P2_12_12_1$, to choose origins for the three principal projections at the points of intersection of the corresponding twofold screw axes with the respective planes of projection. Hence, the origins of the (001), (100), and (010) projections are at the points $(\frac{1}{4}00)$, $(0\frac{1}{4}0)$, and $(00\frac{1}{4})$, respectively, in the co-ordinate system of the "Internationale Tabellen zur Bestimmung von Kristallstrukturen" (Gebr. Borntraeger, Berlin, 1935). For the sake of uniformity all co-ordinates mentioned in the following discussion are referred to the origin $(\frac{1}{4}00)$.

The length of the c axis permits only a single molecule to be accommodated along [001], with the molecular plane inclined at about 45° to (001). For additional information as to the molecular orientation, packing considerations are not very helpful because of the similarity of the a and b axes and the relatively symmetrical shape of the molecule; nor is the level of the unitary structure factors sufficiently high to favour the use of any of the analytical methods of sign determination. The correct molecular orientation was eventually derived by arguments based mainly on the molecular Fourier transform method and on the interpretation of the pseudo-absences in the zonal reflections.

In applying the Fourier transform method we have followed the procedure outlined by Klug (*Acta Cryst.*, 1950, **3**, 176) in the analogous instance of triphenylene and shall therefore restrict the following discussion to features peculiar to the present problem. The real and imaginary parts of the Fourier transform of 3 : 4-benzophenanthrene were calculated on the

assumption of a planar molecule with atoms at the corners of regular hexagons of side 1·40 Å. The system of molecular axes is shown in Fig. 1.

Comparison of the weighted reciprocal lattice with the Fourier transform led to the conclusions that (1) a^* must lie along the *OL* axis of the transform, (2) b^* must lie at about 45° to the plane of the transform, (3) the approximate co-ordinates (u_0, v_0) of the molecular reference point *O* are either (0·01, 0·25) or (0·26, 0·25), (4) the poor agreement between the Fourier transform and observed values of the structure factors beyond the low orders of F(*hk*0) suggests that the planar and regular model used for the computation of the transform represents only inadequately the structure of the real molecule.

A second clue to the molecular orientation is provided by the pseudo-absences in the *h*0*l* zone, which imply that the *b* axis projection of the unit cell approximates to that of space-group $Pmn2_1$ (Figs. 2, *a* and *b*). There are two possible molecular arrangements in $P2_12_12_1$ satisfying this condition of additional symmetry, of which one can be decisively

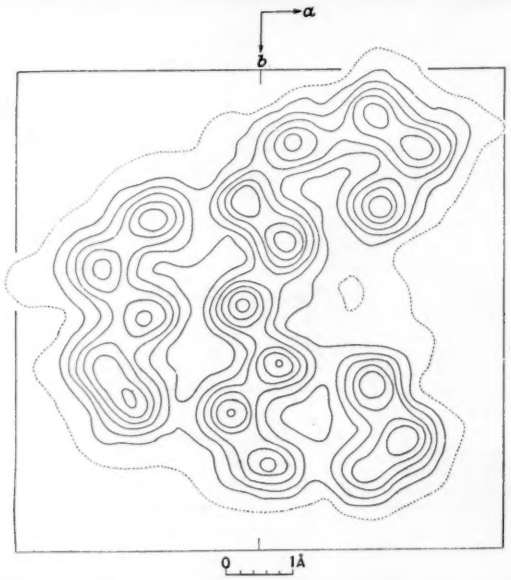


FIG. 3. *The electron-density projection on* (001), *calculated with* 144 *out of* 154 *observed terms. The contours are drawn at intervals of* 1 e.Å^{-2}, *with the one-electron line dotted.*

ruled out. This orientation (Fig. 2, *c*) requires the projected molecule to have a pseudo-centre of symmetry at the point $u = 0$, $w = 0$. As the only possible centrosymmetric projection of benzophenanthrene is that down the molecular *OL* axis it follows that *OL* would necessarily lie parallel to *b*. This arrangement is contradicted by the evidence of the Fourier transform, according to which *OL* is parallel to *a*. Moreover, it is ruled out by the value of F(230), which it would require to be small whereas in fact this reflection is the second strongest in the (*hk*0) zone. In his discussion of possible space-groups Iball put forward this molecular arrangement in $P2_12_12_1$ as the explanation for the extra *h*0*l* absences; he rejected it as an unlikely packing arrangement and concluded that the space-group could not be $P2_12_12_1$.

The second possible molecular arrangement (Fig. 2, *d*) requires the projected molecule to have a pseudo-mirror plane parallel to (001) at $w = 0{\cdot}25$. This must coincide with the projected *OL* axis, evidently a molecular twofold axis of symmetry. Thus, the information deduced from the pseudo-absences, together with the evidence from the Fourier transform, leads to the following conclusions: (1) the molecule has an approximate twofold axis of symmetry along *OL*, nearly parallel to the *a* axis; (2) *OM* is inclinded at about 45° to the *a* axis; (3) the approximate co-ordinates of the point *O* are $u_0 = 0{\cdot}01$ or $0{\cdot}26$ (Fourier transform), $v_0 = 0{\cdot}25$ (Fourier transform), $w_0 = 0{\cdot}25$ (*h*0*l* pseudo-absences).

Conditions (1) and (3) together imply that the symmetry of the cell approximates to that of space-group $B22_12$; we should thus expect the pseudo-absences to extend throughout the reciprocal lattice. Indeed, Weissenberg photographs of the *hk*1 and *hk*4 spectra as well as of the three principal zones reveal that reflections with $h + l$ odd tend to be generally weaker than those with $h + l$ even.

The ambiguity in the u_0 parameter was resolved in favour of $u_0 = 0{\cdot}01$ from considerations of molecular packing; during the course of the analysis the second alternative was tested and ruled out on the basis of the *h*0*l* structure factors.

Atomic co-ordinates were calculated for a planar and regular molecule with $u_0 = 0{\cdot}01$, $v_0 = 0{\cdot}25$, $w_0 = 0{\cdot}25$, *OL* parallel to [100], and *OM* at 45° to (001). Refinement from this original set of co-ordinates was carried out by means of successive $F_O - F_C$ syntheses until the *R* factor had decreased to 0·22. There remained at this stage ten *hk*0 structure factors

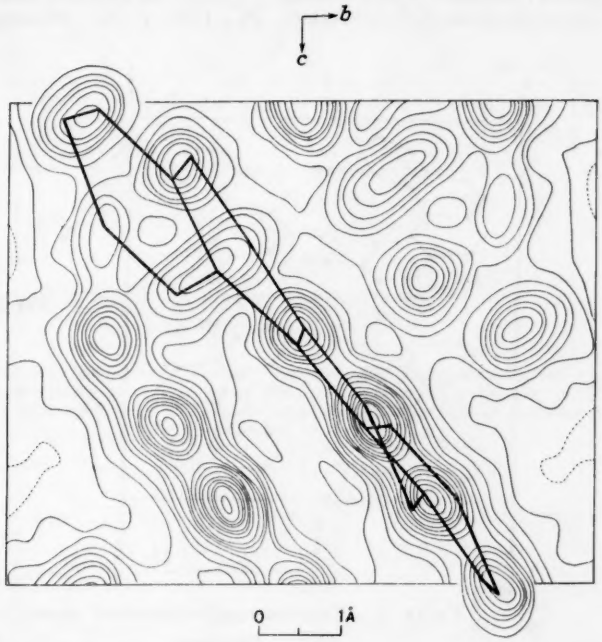


FIG. 4. *The electron-density projection on* (100).

of uncertain sign, of which six had unitary scattering factors exceeding 0·05, the largest being U(14,2,0) = 0·16. However, as a further difference synthesis failed to improve the agreement for these reflections it was concluded that the atomic co-ordinates already determined were the best that could be derived from the present experimental data.

A Fourier summation of 144 terms, out of 154 observed, was calculated at intervals of 120ths along *a* and *b* (Fig. 3). This projection shows that the molecule is not regular and probably not planar. By means of an adjustable wire model a non-planar molecular configuration was fitted to this projection, in which the mean plane of the molecule was inclined at about 45° to the projection plane. With the molecular reference point *O* located at $w_0 = 0{\cdot}25$, approximate *w* co-ordinates were obtained from this model, giving *R* factors for the 0*kl* and *h*0*l* zones of 0·42 and 0·34, respectively. Although the degree of overlap is smaller in the 0*kl* than in the *h*0*l* zone, the latter was refined first because of the smaller initial value of its *R* factor. After five difference syntheses *R*(*h*0*l*) had been reduced to 0·18; however, *R*(0*kl*) had risen to 0·47 and this set of *w* co-ordinates was therefore discarded.

Adjustment of the initial set of *w* co-ordinates produced a new molecular model which

gave values of $R(0kl)$ and $R(h0l)$ of 0·26 and 0·30 for reflections up to $2 \sin \theta = 1{\cdot}0$. Refinement of this model by difference syntheses on the $0kl$ reflections resulted after eight cycles in values for $R(0kl)$ and $R(h0l)$ of 0·023 and 0·26, at which point refinement ceased. The final Fourier projection on to (100), embodying 58 of the 62 observed $0kl$ structure factors, is shown in Fig. 4, and Table 1 lists the final z co-ordinates in col. 4 and the spurious z co-ordinates, derived from the $h0l$ zone only, in col. 5.

No attempt has been made to improve the rather high discrepancy factors (0·22, 0·23, and 0·26 in the $hk0$, $0kl$, and $h0l$ zones), which may be partly due to the exclusion of the hydrogen contributions from the calculated structure factors. That these contributions are not insignificant is shown by the appearance of a (001) projection obtained by one of us on *X*-RAC; this summation contains all observed $hk0$ structure factors, including the ten terms referred to above, whose signs were determined by means of the "negative-background criterion" (*e.g.*, Pepinsky, "Computing Methods and the Phase Problem in *X*-Ray Crystal Analysis," State College, Pa., 1952, p. 3). Although the carbon peaks are not

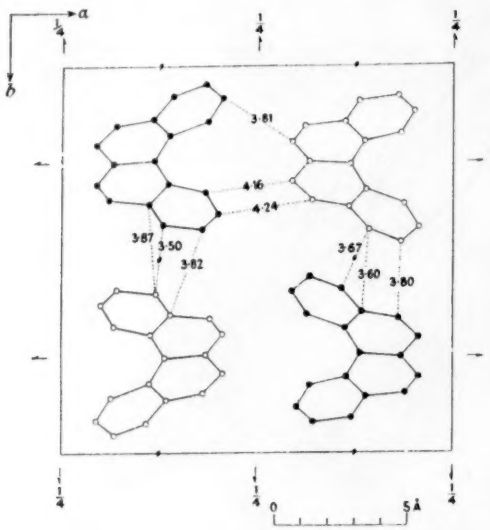


FIG. 5. *The projection of the unit-cell contents on* (001).

TABLE 1. *Experimentally-determined atomic co-ordinates (in* Å).

Atom *	x	y	z	Spurious z co-ordinates	Atom *	x	y	z	Spurious z co-ordinates
1	1·81	2·06	0·86	0·94	10	1·60	5·97	4·46	4·06
2	2·39	1·18	0·05	−0·02	11	2·19	5·43	3·34	2·86
3	1·70	0·65	−1·25	−1·10	12	1·73	4·64	2·40	2·00
4	0·50	1·08	−1·38	−1·38	13	0·40	2·54	0·58	0·71
5	−1·63	2·19	−0·79	−0·74	14	−0·24	1·94	−0·54	−0·46
6	−2·38	2·89	0·21	0·63	15	0·32	4·31	2·46	2·30
7	−2·38	4·34	2·19	2·31	16	−0·41	5·05	3·25	3·29
8	−1·90	4·91	3·44	3·31	17	−0·22	3·46	1·45	1·57
9	0·12	5·82	4·30	4·16	18	−1·75	3·58	1·25	1·46

* Cf. Fig. 1 and footnote, p. 3303.

significantly affected by these ten additional terms, the molecular outline is altered in the regions where hydrogen peaks may be expected. It is hoped later to refine this structure by a low-temperature technique whose usefulness as regards both accurate bond lengths and location of hydrogen atoms has been demonstrated in the structure of α-phenazine (Hirshfeld and Schmidt, *Acta Cryst.*, 1954, **7**, 129). In the meantime the general features of the crystal structure and of the molecular shape are quite clear on the basis of the present results.

FIG. 6. *The projection of the unit-cell contents on* (100).

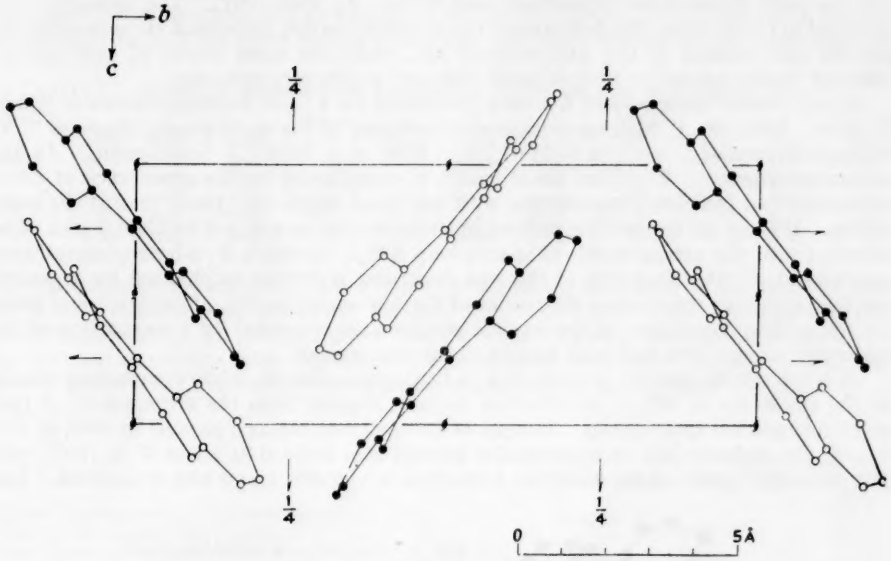


FIG. 7. *The projection of the unit-cell contents on* (010). *In the lower half of the projection two of the overlapping molecules have been omitted for greater clarity.*

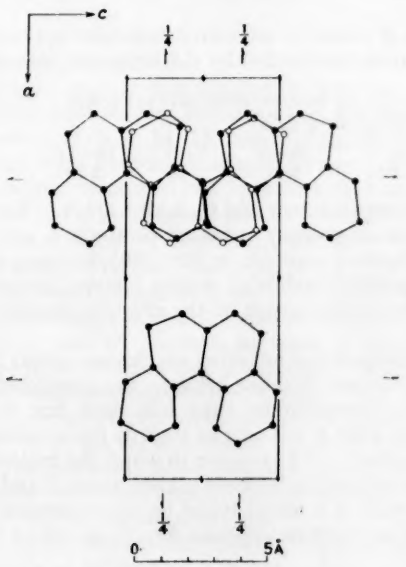
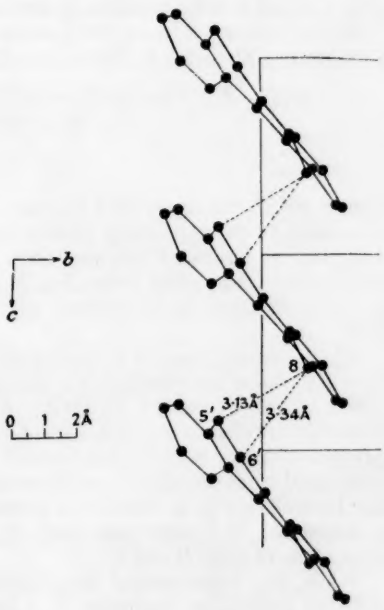


FIG. 8. *The molecular arrangement in one stack along* [001] *seen in the* (100) *projection, showing the short approach distances between neighbouring molecules.*



Despite the non-planarity of 3 : 4-benzophenanthrene, the packing arrangement of the molecule in the cell (Figs. 5—8) is similar to that observed in normal aromatic hydrocarbons such as coronene (Robertson and White, *J.*, 1945, 607). The molecules are arranged in stacks along the short axis of the unit cell; within each stack the molecules are parallel and inclined to this axis at about 40°, while the mean planes of molecules in different stacks, related by twofold screw axes, are nearly perpendicular.

A very similar arrangement has been postulated for 3 : 4-5 : 6-dibenzocarbazole (Iball, *Z. Krist.*, 1936, **95**, *A*, 282), an overcrowded molecule of the same general shape as 3 : 4-benzophenanthrene: *viz.*, $a = 14{\cdot}07$, $b = 6{\cdot}10$, $c = 15{\cdot}36$ Å. Space-group, $A2_122$; molecular symmetry, 2. There the situation is complicated by the appearance of extra reflections that indicate a superlattice with one axial length four times that of the main lattice. If these are ignored the packing of the molecules as deduced by Iball is seen to be identical with the arrangement, in space-group $B22_12$, to which 3 : 4-benzophenanthrene approximates. The similarity of the two structures is further emphasised by a general correspondence in the relative intensities of the low-angle spectra, allowance being made for the cyclic permutation of the crystallographic axes suggested by a comparison of the molecular orientations and axial lengths in the two crystals.

It is interesting that the packing in 3 : 4-benzophenanthrene, while approaching closely to the symmetry of $B22_12$, nevertheless deviates slightly from the arrangement of that more symmetrical space-group. Instead of an exact twofold axis parallel to [100] at $v = w = \frac{1}{4}$, the molecule has an approximate twofold axis inclined at about 7° to [100], with the geometric centre of the molecule located at $u = 0{\cdot}007$, $v = 0{\cdot}243$, $w = 0{\cdot}253$. This

FIG. 9. *The molecular model viewed at about 30° to the twofold axis.*

would appear to indicate that the lattice energy must be critically dependent on the precise disposition of the molecules in the cell; such a situation might be somewhat surprising were it not for certain short intermolecular contacts that also imply the presence of crystal forces unusual in fully aromatic hydrocarbons.

Within each stack along [001], several pairs of atoms in successive molecules approach to within less than 3·7 Å (Table 2). The shortest intermolecular distances are between

TABLE 2. *Some short contact distances (in* Å*) between molecules separated by unit translation along the* c *axis.*

Atoms	8—5′	8—6′	16—5′	7—5′	16—14′
Distance	3·13	3·34	3·48	3·55	3·70

atoms 8 and 5′, which are 3·13 Å apart, and between atoms 8 and 6′, 3·34 Å apart. These close contacts are apparently related to an unusual valency structure of atoms 5 and 8, which will be discussed further below. The shortest contacts in the [100] direction are greater than those along [010] (Fig. 5); this probably indicates weaker binding forces in the [100] direction, in accordance with the observed cleavage of the crystals parallel to {100}.

At the present stage of crystallographic refinement the following conclusions about the molecular shape are warranted. The centre-to-centre distance between the overcrowded carbon atoms 1 and 12 is 3·0 Å; 3 : 4-benzophenanthrene thus falls into line with previously-studied overcrowded compounds (see Part I, *loc. cit.*) as regards the minimum approach distance between non-bonded carbon atoms. The manner in which the molecule is distorted from planarity so as to achieve this separation between carbon atoms 1 and 12 may be seen in Fig. 9, which is a perspective view of a model based on the experimental co-ordinates. It is seen that rings *A* and *A′* are bent in opposite directions out of the mean plane of rings *B* and *B′*.

While the experimental co-ordinates do not conform precisely to the chemically-probable molecular symmetry 2, a molecule having exact twofold symmetry may be

visualised, whose atomic co-ordinates, listed in Table 3, deviate from the experimental values by a root-mean-square difference of only 0·03 Å. This deviation is probably not significant, since structure factors calculated for the symmetrical model lead to R factors for the $hk0$, $0kl$, and $h0l$ zones of 0·23, 0·25, and 0·27, which are not much higher than for

TABLE 3. *Atomic co-ordinates (in* Å*) adjusted to conform with molecular symmetry* 2.

Atom	x	y	z	Atom	x	y	z	Atom	x	y	z
1	1·76	2·05	0·85	7	−2·43	4·34	2·19	13	0·40	2·54	0·54
2	2·32	1·18	0·03	8	−1·88	4·93	3·38	14	−0·24	1·92	−0·47
3	1·76	0·68	−1·23	9	0·18	5·80	4·31	15	0·33	4·32	2·42
4	0·44	1·07	−1·36	10	1·55	6·01	4·46	16	−0·42	5·03	3·30
5	−1·63	2·21	−0·84	11	2·27	5·42	3·32	17	−0·22	3·47	1·42
6	−2·33	2·88	0·22	12	1·77	4·62	2·39	18	−1·76	3·57	1·27

the experimental co-ordinates. Accordingly, in discussing the shape of the molecule and the manner in which it is deformed, we shall refer exclusively to the dimensions of the symmetrical model. On the assumption that the molecule does in fact possess symmetry 2, the observed deviations from this symmetry provide an estimate of the accuracy of the present analysis. Thus the experimental co-ordinates may be regarded as subject to a

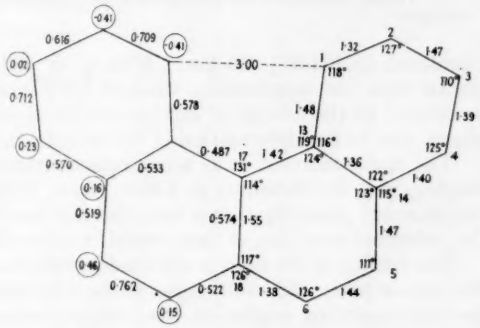


FIG. 10. *Dimensions of the symmetrical model fitted to the experimental co-ordinates. The bond lengths (in* Å*) and the bond angles are indicated on the right, the theoretical mobile bond orders (Berthier* et al., loc. cit.*) on the left. The circled figures are the distances of the atoms from a reference plane through atoms* 13, 15, 17, 18.

root-mean-square error of 0·05 Å, which is then also the root-mean-square error of the averaged bond lengths (except for bond 17—18, which occurs only once) shown in Fig. 10.

The most striking feature of this structure is the non-planarity of the " benzene " rings. Atoms 1, 2, 3, 4, 14, 13, constituting ring A, deviate from the best plane through these atoms by a root-mean-square distance of over 0·05 Å and a maximum of 0·08 Å, the deviations being systematic so that the ring may be regarded as folded, through an angle of 10°, along the diagonal joining atoms 3 and 13. The distortion of ring B is even greater, its atoms deviating from their best plane by a root-mean-square distance of 0·08 Å and a maximum of 0·10 Å. Here again the principal mode of deformation consists in a folding of the ring, through an angle of 14° along the diagonal 5—17. It seems certain that this folding of rings A and B, together with the corresponding folding of the symmetry-related rings A' and B', accounts for most of the distortion of the molecular skeleton by which relief from overcrowding is achieved. Any other deformations of the skeleton appear to be of secondary importance, atoms 1, 2, 3, 4 being coplanar to within a root-mean-square deviation of 0·02 Å, while the groups comprising atoms 3, 4, 14, 5, 17, 13 and atoms 5, 6, 18, 7, 8, 17 are each planar to within a root-mean-square deviation of 0·04 Å.

The molecular properties likely to be affected by the distortions of the aromatic system include resonance energy, dipole moment, valency structure, and chemical reactivity; these will be discussed in turn.

The results of calculations, by the method of molecular orbitals, of theoretical resonance energies of all four-ring aromatic hydrocarbons $C_{18}H_{12}$ (Berthier, Coulson, Greenwood, and A. Pullman, *Compt. rend.*, 1948, **226**, 1906) are quoted in Table 4. The computations, for planar molecules, were made both with and without allowance for overlap between

adjacent atomic orbitals, the results being given in terms of the empirical constants γ and β respectively. The corresponding experimental values have been determined by Magnus and Becker (*Erdöl und Kohle*, 1951, **4**, 115). By combining the theoretical and experimental results for all these compounds except 3 : 4-benzophenanthrene, we obtain values for γ and β of 37·64 $\pm$ 1·0 kcal./mole and 18·61 $\pm$ 0·15 kcal./mole, respectively. The resonance energy per mole of the planar model of 3 : 4-benzophenanthrene is thus

TABLE 4. *Comparison of experimental and theoretical resonance energies of all four-ring aromatic hydrocarbons* $C_{18}H_{12}$.

Compound	Exptl. resonance energy (kcal./mole) *	Quantum-mechanical resonance energy : † with overlap (γ)	without overlap (β)	γ ‡ (kcal./mole)	β ‡ (kcal./mole)	Quantum-mechanical resonance energy : γ = 37·64	β = 18·61
3 : 4-Benzophenanthrene	127·7	3·5840	7·1874	35·63	17·77	134·9	133·8
Tetracene	129·6	3·3400	6·9316	38·80	18·70	125·7	129·0
1 : 2-Benzanthracene ...	130·4	3·5027	7·1012	37·23	18·36	131·8	132·2
Chrysene	134·4	3·5872	7·1900	37·47	18·69	135·0	133·8
Triphenylene	135·8	3·6658	7·2745	37·05	18·67	138·0	135·4

* Magnus and Becker, *loc. cit.* † Berthier *et al.*, *loc. cit.*
‡ Values derived from comparison of corresponding experimental and theoretical resonance energies.

calculated as 134·9 $\pm$ 3·5 kcal., from γ, or 133·8 $\pm$ 1·1 kcal., from β; both values are greater than the experimental value of 127·7 kcal. The energy defect of 6 or 7 kcal. must be related to the energy of intramolecular repulsion, neglected in the theoretical calculations, and to the deformation of the hypothetically-planar ring system.

The dipole moment of 3 : 4-benzophenanthrene has been reported as 0·7 D (Bergmann, Fischer, and B. Pullman, *J. Chim. phys.*, 1951, **48**, 356). The major contribution to this moment probably comes from the dipoles of the C–H bonds, which do not cancel in the deformed structure as they would in a regular planar molecule.

The folding of the rings is reflected in the abnormal bond angles at the carbon atoms on the axes of fold; the bond angles at the secondary atoms 3 and 5 are 110° and 111°, while the corresponding angles at the tertiary carbon atoms 13 and 17 are 116° and 114°. Although the individual values may not be too reliable, it is significant that they all deviate in the same direction from the trigonal bond angle of 120° and that those at the secondary carbon atoms approach the tetrahedral angle of 109½°. Thus it appears that the valency electrons of these secondary atoms do not occupy pure $(sp^2)p$ orbitals, appropriate to a planar aromatic structure, but more nearly approximate to the tetrahedral sp^3 hybridisation. This must imply an enhanced localisation of the π electrons that these atoms contribute to the aromatic system and may be expressed in a greater polarisability than would be expected in an undeformed molecule. Whether or not this localisation involves a decoupling of the electron spins should be deducible from magnetic data, which are unfortunately not available. A knowledge of the hydrogen positions would be of considerable value in specifying more exactly the type of hybridisation present.

The increased free valence that may be expected to accompany the apparent shift towards tetrahedral hybridisation probably accounts for the short approach distance between atoms 5 and 8 of neighbouring molecules in the crystal, which may indicate a tendency towards additional bond formation on the part of these " unsaturated " atoms. On the basis of the co-ordinates of the symmetrical model it is found that the line joining atoms 5 and 8 of neighbouring molecules makes, at one end, angles of 85° and 112° with bonds 5–6 and 5–14 respectively and, at the other end, angles of 94° and 91° with bonds 8–7 and 8–16 respectively.

The known chemical properties of 3 : 4-benzophenanthrene support the above view of the valency structure since the increased availability of negative charge at the distorted carbon atoms provides an explanation for the preferential substitution at the 5-position by bromine, nitric acid, and the Friedel–Crafts reagent (Newman and Kosak, *J. Org. Chem.*, 1949, **14**, 375). Also the tetrahedral hybridisation already evident at the reactive carbon

atom in the unperturbed molecule would favour the formation of the activated complex, in which, supposedly, the entering substituent and the outgoing hydrogen are simultaneously bound to this carbon atom in a tetrahedral arrangement (*e.g.*, Waters, *J.*, 1948, 727). We

TABLE 5. *List of observed and calculated structure factors.*

(*a*) F(*hk*0) referred to origin ($\frac{1}{4}$00).

*hk*0	F_o	F_c *	*hk*0	F_o	F_c *	*hk*0	F_o	F_c *	*hk*0	F_o	F_c *
200	67†	102	10,30	3	− 5	180	9	− 8	1,12,0	7	5
4	49	−48	11	5	− 8	2	0	1	2	11	8
6	61	63	12	0	− 2	3	6	−10	3	7	5
8	51	63	13	0	− 1	4	0	4	4	0	− 1
10	5	5	14	4	− 3	5	0	2	5	3	− 3
12	7	− 9	15	0	1	6	0	− 3	6	3	− 2
14	12	−13	16	3	5	7	0	1	7	3	− 1−
16	4	− 4				8	7	6	8	5	7
			140	15	−11	9	10	−10	9	6	7
020	56	−69	2	24	−20	10	7	3	10	2	6
4	56	−60	3	11	− 8	11	3	− 6	11	0	3
6	0	2	4	13	10	12	0	− 2	12	3	− 5
8	16	−14	5	9	2−	13	2	1+	13	4	− 4
10	12	−12	6	12	−12	14	3	7	14	2	− 4
12	13	13	7	0	− 3	15	0	− 2			
14	4	3	8	13	−15	16	3	6	1,13,0	6	4
16	5	2−	9	8	− 1+				2	0	− 2
18	9	−13	10	0	2	190	8	− 8	3	0	− 2
			11	2	− 2	2	20	15	4	0	0
			12	3	4	3	0	− 3	5	5	5
110	9	6				4	27	24	6	5	6
2	12	11				5	0	0	7	2	3
3	6	− 3	150	0	22	6	13	12	8	5	− 7
4	16	−16	2	15	−13	7	0	− 2	9	4	− 5
5	0	0	3	2	3	8	11	10			
6	4	− 4	4	6	− 9	9	0	− 1	1,14,0	0	− 1
7	4	− 5	5	0	− 2	10	17	21	2	0	1
8	4	4	6	5	− 4	11	0	1	3	0	2
9	0	− 5	7	0	2	12	13	17	4	0	1
10	6	− 6	8	3	− 3	13	0	1	5	0	1
11	2	− 1				14	5	6	6	0	1
12	0	− 4	160	5	− 5	15	0	2	7	7	− 8
13	3	− 5	2	4	− 3	16	4	4	8	0	− 1
14	5	3	3	7	− 3−				9	3	− 5
			4	15	−11	1,10,0	3	3			
			5	2	5	2	12	− 9	1,15,0	0	1
120	9	− 5	6	6	− 6	3	5	− 4	2	0	1
2	17	−20	7	4	2	4	12	11	3	0	− 2
3	2	0−	8	5	4	5	0	1	4	0	2
4	3	2	9	6	1−	6	13	13	5	0	− 2
5	5	− 4	10	5	− 2−	7	17	20	6	0	− 1
6	21	−23	11	6	1−	8	14	−16	7	0	2
7	18	−17	12	10	− 8	9	5	7	8	2	1
8	17	−13				10	6	− 9	9	0	1
9	11	− 9				11	6	− 7	10	3	3
10	0	1	170	5	3	12	12	14			
11	0	4	2	6	1+	13	3	3	1,16,0	2	− 2
12	3	1+	3	7	10	14	3	4	2	2	2
13	4	5	4	24	−23	15	5	9	3	0	0
14	7	1+	5	7	− 7				4	3	4
15	4	4	6	6	− 4	1,11,0	12	−12	5	2	2
			7	4	− 1+	2	0	0			
			8	2	5	3	0	2	1,17,0	0	1
130	13	14	9	13	18	4	6	− 6	2	0	1
2	68	−77	10	17	−18	5	4	6	3	9	11
3	20	−16	11	9	9	6	0	2	4	0	− 1
4	16	13	12	12	−12	7	6	− 7	5	4	5
5	7	− 5	13	0	− 1	8	0	1			
6	19	23	14	0	4	9	11	−13	1,18,0	0	0
7	9	9	15	0	4	10	8	− 9	2	6	− 6
8	11	−14	16	0	− 1	11	2	− 5			
9	8	− 2−	17	3	6	12	3	− 2			

* Signs determined on *X*-RAC by means of the " negative-background criterion."
† Presumed secondary-extinction error.

TABLE 5. (*Continued.*)

(*b*) F(0*kl*) referred to origin (0¼0).

0*kl*	Fo	Fc	0*kl*	Fo	Fc	0*kl*	Fo	Fc	0*kl*	Fo	Fc
002	13	−11	012	8	−10	073	0	1	015	10	15
4	0	3	2	20	20	8	6	−10	2	3	7
6	12	−20	3	11	10	9	18	−16	3	0	− 4
			4	23	−24	10	8	5	4	0	1
			5	35	34	11	11	− 9	5	8	6
011	0	− 2	6	43	−40	12	8	5			
2	10	13	7	26	26				016	0	− 2
3	8	−11	8	9	− 5				2	3	− 6
4	14	− 5	9	3	− 3	014	0	− 2	3	0	1
5	25	18	10	8	−13	2	12	−15	4	3	4
6	27	−23	11	18	−18	3	5	− 2	5	0	− 1
7	6	7	12	9	−12	4	15	17	6	0	− 1
8	9	11	13	6	− 9	5	14	19	7	0	1
9	0	− 1				6	30	37	8	0	1
10	4	1				7	14	15	9	4	2
11	8	6	013	10	−11	8	0	− 2			
12	0	1	2	2	4	9	9	− 4	017	0	5
13	0	− 1	3	7	6	10	0	− 4	2	0	2
14	8	8	4	10	− 7	11	8	− 8	3	0	− 2
15	5	− 5	5	10	8	12	11	7	4	0	2
			6	8	− 5	13	7	− 6	5	5	−10

(*c*) F(*h*0*l*) referred to origin (00¼).

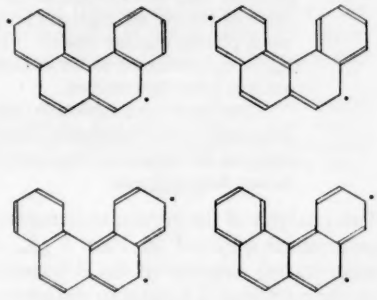
*h*0*l*	Fo	Fc	*h*0*l*	Fo	Fc	*h*0*l*	Fo	Fc	*h*0*l*	Fo	Fc
101	24	24	402	7	2	803	0	3	105	3	7
2	3	− 2	5	0	1	9	20	20	2	5	− 4
3	8	−13	6	16	19	10	0	− 2	3	6	− 7
4	0	− 2	7	0	− 5	11	25	−28			
5	7	− 9	8	11	16	12	0	− 1	106	0	1
6	8	− 7	9	5	− 7	13	6	6	2	11	−10
7	4	− 4	10	15	−16				3	0	3
8	6	6	11	6	9	104	0	− 5	4	9	5
9	0	2				2	0	− 5			
10	0	1	103	19	19	3	6	− 7			
11	5	1	2	2	− 9	4	0	7	506	0	2
			3	46	−42	5	0	0	6	3	− 5
			4	4	− 2	6	0	− 3	7	0	− 1
102	4	− 2	5	28	19	7	0	2	8	3	6
2	36	−27	6	0	4	8	0	− 1			
3	3	9	7	0	3	9	8	5			

prefer this explanation to the one based on an analogy with the reactivity of phenanthrene at the 9-position, which would in any case not account for the preferential attack on the 5- rather than the 6-position in 3 : 4-benzophenanthrene. Two disubstitution products were also found in the nitration reaction but their constitution was not investigated further. Unless primary substitution fundamentally changes the structure of the molecule we should expect, on the above arguments, that the second substituent has entered at the 8-, 3-, or 10-position.

Although the present bond-length measurements are not sufficiently accurate to warrant detailed analysis, their general tendency is in accord with the proposed interpretation of the molecular valency structure. Some idea of the bond lengths to be expected on this hypothesis may be derived from a consideration of the eight biradical structures (Fig. 11) suggested by the tetrahedral bond angles at atoms 3, 5, 8, and 10. Although there is no evidence that the molecule is, in fact, a biradical, we should expect similar bond-length variations to occur even if the electron spins are not uncoupled since there are one Dewar long-bond and two ionic structures corresponding, in the distribution of single and double bonds, with each of the proposed biradical structures and these would probably contribute strongly, along with the eight Kekulé-type structures, to the resultant bond structure of a molecule with no unpaired electrons. Thus, the length of the central 17–18 bond, which is certainly exaggerated by the present data, is partly explained by the fact that it appears single in all the suggested non-Kekulé formulæ, as does bond 5–14, whose measured length

is 1·47 Å. These formulæ would also indicate three-fourths double-bond character for bond 1–2, measured as 1·32 Å long. It may also be significant that bond 5–6, with a measured length of 1·44 Å despite its theoretical mobile-bond order of 0·762 calculated by Berthier *et al.* (*loc. cit.*), for a planar molecule, appears as a double bond in just half the biradical, or pseudo-biradical, formulæ under consideration. Thus the measured bond lengths, insofar as they are reliable, seem generally consistent with the other evidence as to the type of electronic structure to be associated with the distorted benzophenanthrene molecule.

FIG. 11. *Four of the eight biradical formulæ suggested by the tetrahedral bond configurations. The remaining four are related to these by the operation of the molecular two-fold axis of symmetry.*



The conclusions reached here provide a coherent interpretation of the known physical and chemical properties of 3 : 4-benzophenanthrene, as well as indicating several directions in which further work is needed. On the crystallographic side, comparison of these results with the analysis of the crystal structure of 5 : 4′-dimethyl-3 : 4-benzophenanthrene, which is already well under way, will be of particular interest.

The crystallographic evidence indicates resolution of 3 : 4-benzophenanthrene into (+)- and (−)-crystals. We have not yet succeeded in growing crystals either of large enough size or with sufficiently well-developed *hkl* faces to take advantage of this spontaneous resolution for the measurement of the optical activity of 3 : 4-benzophenanthrene; experiments in this direction are in progress.

Experimental.—Good crystals of 3 : 4-benzophenanthrene can be obtained by slow cooling of a solution in ethanol. They are colourless needles, elongated along [001], whose most prominent faces are {100} and {010}, with {110} and {011} frequently present. The crystals show a cleavage plane parallel to {100}.

All zonal reflections obtainable with Cu-$K\alpha$ radiation were recorded on Weissenberg photographs about the three principal axes, and their intensities measured visually by comparison with a series of standard spots. The roughly cylindrical outline of the crystals made spot-shape and absorption corrections in the *hk*0 zone unnecessary; for photographs about the [100] and [010] axes, a crystal was cut to approximately cubic shape. The absolute scale, originally estimated by Wilson's statistical method (*Nature*, 1942, **150**, 151), was later found, on comparison with the scale of the final calculated structure factors, to be about 10% higher in F(*hkl*) that the scale originally adopted. The accuracy of the observed structure factors is thought to be of the order of 10%.

We are grateful to Professor M. S. Newman and to Dr. J. Szmuskowicz for gifts of crystals of 3 : 4-benzophenanthrene, and to Mr. F. L. Hirshfeld for many helpful suggestions during the preparation of this paper. One of us (G. M. J. S.) is greatly indebted to Professor R. Pepinsky for the use of *X*-RAC, and to the Rockefeller Foundation for financial support, during his stay at State College, Pa. We also acknowledge the help of Mr. B. Smilovits with the calculations and of Mr. R. Cohen with the preparation of the diagrams. This work was carried out during the tenure of the Porter scholarship of the University of Cape Town.

THE LABORATORY OF *X*-RAY CRYSTALLOGRAPHY,
THE WEIZMANN INSTITUTE OF SCIENCE, REHOVOTH, ISRAEL. [*Received, January 11th*, 1954.]

The Structure of Overcrowded Aromatic Compounds. Part IV. The Crystal Structure of Tetrabenzonaphthalene.*

By F. H. Herbstein and G. M. J. Schmidt.

[Reprint Order No. 5062.]

A partial analysis of the crystal structure of tetrabenzonaphthalene has been carried out by two-dimensional Fourier methods. The molecular position and orientation in the $h0l$ zone were determined by the interpretation of the strong high-angle spectra and of the Fourier transform calculated for a planar regular model. The (010) projection was refined by successive $F_o - F_c$ syntheses to an R factor of 0·22. The third set of co-ordinates has not yet been determined.

The projected molecular dimensions rule out a planar centrosymmetric structure; it is suggested that the molecular symmetry is 222, and that the type of distortion of the aromatic nucleus is similar to that found in 3 : 4-benzophenanthrene.

The analysis of the crystal structure of tetrabenzonaphthalene (Fig. 1) is part of a research programme outlined in Part I (*J.*, 1954, 3288). The primary aim is to obtain some quantitative measure of the deformation of representative overcrowded molecules caused by the retention of minimum distances of approach between non-bonded atoms. Formally, the nature of overcrowding in tetrabenzonaphthalene and 3 : 4-benzophenanthrene (Part III *) is very similar, and it is therefore of interest to compare the mechanisms of the relief of overcrowding in the two molecules. However, the crystal structure of tetrabenzonaphthalene is not readily investigated by two-dimensional methods, since only one zone gives a reasonably clear view of the molecule, the other two zones being completely overlapped. As the three-dimensional analysis must be delayed, we present the preliminary results of a partial two-dimensional analysis now, although only the broad outlines of the crystal and molecular structure are available.

The dimensions of the unit cell, and in particular the length of the b axis, suggest that the molecules are arranged in a two-layer structure with the molecular planes inclined at about 25° to the (010) plane. On the assumption that the molecule is approximately planar and has atoms placed at the corners of regular hexagons of side 1·40 Å, one may expect groups of strong spectra at about 120° to one another with interplanar spacings of 1·2 and 2·1 Å, respectively, as these distances correspond to prominent periodicities of the molecule (cf. Robertson and White, *J.*, 1945, 607). Table 1 lists the strongest high-

Table 1. *List of strong, high-angle spectra.*

$h0l$	d (Å)	U($h0l$)	$h0l$	d (Å)	U($h0l$)	$h0l$	d (Å)	U($h0l$)	$h0l$	d (Å)	U($h0l$)
602	2·20	0·24	$20\bar{5}$	2·33	0·28	208	1·23	0·25	14,0,II	1·06	0·34
801	2·00	0·40	$80\bar{4}$	2·37	0·23	408	1·14	0·31	$16,0\bar{2}$	1·22	0·53
			$10,0\bar{4}$	2·00	0·46	608	1·04	0·27	$16,0\bar{3}$	1·25	0·41
									$18,0\bar{3}$	1·10	0·38

angle spectra together with the values of the interplanar spacings and unitary structure factors. The results limit the possible orientations to the three shown in Fig. 2. A choice among these three orientations was effected by means of the molecular Fourier transform, which was calculated for a planar and centrosymmetric model with atoms placed at the corners of regular hexagons of side 1·40 Å.

The net of the weighted reciprocal lattice was adjusted to the plot of the Fourier transform in accordance with each of the three molecular orientations deduced from the high-angle spectra. Orientations I and III were eliminated immediately by comparison of the Fourier-transform values with the observed $h00$ structure factors. Values of $u_0 = 0{\cdot}013$, $w_0 = 0{\cdot}354$ corresponding to orientation II were calculated by comparison of the measured and the transform values of the geometrical structure factors, after slight adjustment of

* Part III, preceding paper.

the molecular orientation had produced the best agreement between them. With these values the phase factors $\cos 2\pi (hu_0 + lw_0)$ were calculated, and the signs of the *h*0*l* structure factors derived. Some of these signs were unreliable because of the small values of their phase factors or because the reciprocal-lattice points lay in regions where the sign of the Fourier transform changed rapidly; however, 108 of the 171 observed terms were considered sufficiently reliable to be incorporated into a first Fourier projection on to the (010) plane. Of these 108 signs actually only 64 were found to be correct when compared with the signs calculated from the final set of atomic co-ordinates. The greater number of signs deduced incorrectly here, as compared for example with α-phenazine (Herbstein and Schmidt, *Nature*, 1952, **169**, 323), is due mainly to errors in the (u_0, w_0) co-ordinates; the final co-ordinates (0·009, 0·383) of the molecular reference point *O* are in only fair agreement with the original estimate. A further source of error lies in the initial assumptions

FIG. 1. *The planar model of the tetrabenzonaphthalene molecule, showing the molecular axes and the nomenclature of atoms.*

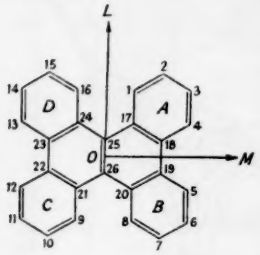
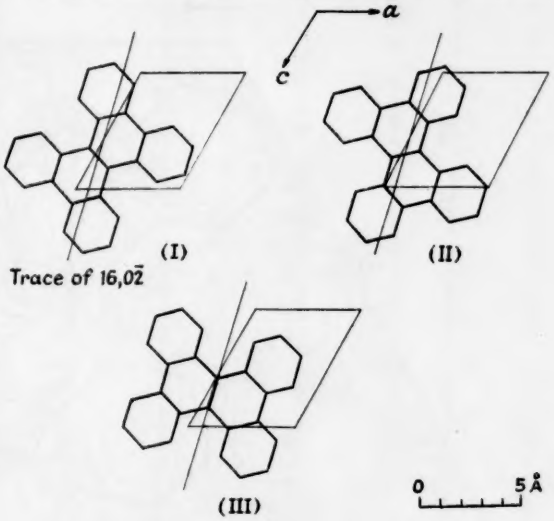


FIG. 2. *The three possible orientations of the molecule, projected on to* (010), *as deduced from the high-angle spectra. The trace of* 16,0$\bar{2}$, *passing through the subsequently-determined position of the molecular centre, has been inserted to act as reference line.*



about the molecular shape; the molecule is in fact not planar, regular, or centrosymmetric. However, the error in the *h*0*l* structure factors due to the incorrect molecular shape assumed in the calculation of the Fourier transform is reduced by the small inclination of the molecular plane to the plane of projection (cf. the similar situation in dianthronylidene; Harnik and Schmidt, Part II, *J.*, 1954, 3295).

The Fourier projection on to (010) gave a recognisable view of the molecule, although only 13 out of the 26 crystallographically independent atoms were resolved. A first refinement of this projection was carried out by three further Fourier syntheses, the unresolved atoms being placed on the assumption of a regular and planar molecule. Further refinement, without assumptions about molecular shape, was achieved by $F_O - F_C$ syntheses. After four cycles the *R* factor had been reduced to 0·22, whereupon refinement ceased although there remained 26 terms of uncertain sign, of which 14 had unitary structure factors >0·05. It is probable that 171 reflections are too few to allow of the complete refinement of a zone where 52 parameters are to be determined. The atomic co-ordinates from the final difference synthesis are listed in Table 2; the signs of the structure factors calculated from these co-ordinates (Table 3) were used in the summation of the Fourier series shown in Fig. 3, in which 145 terms were included.

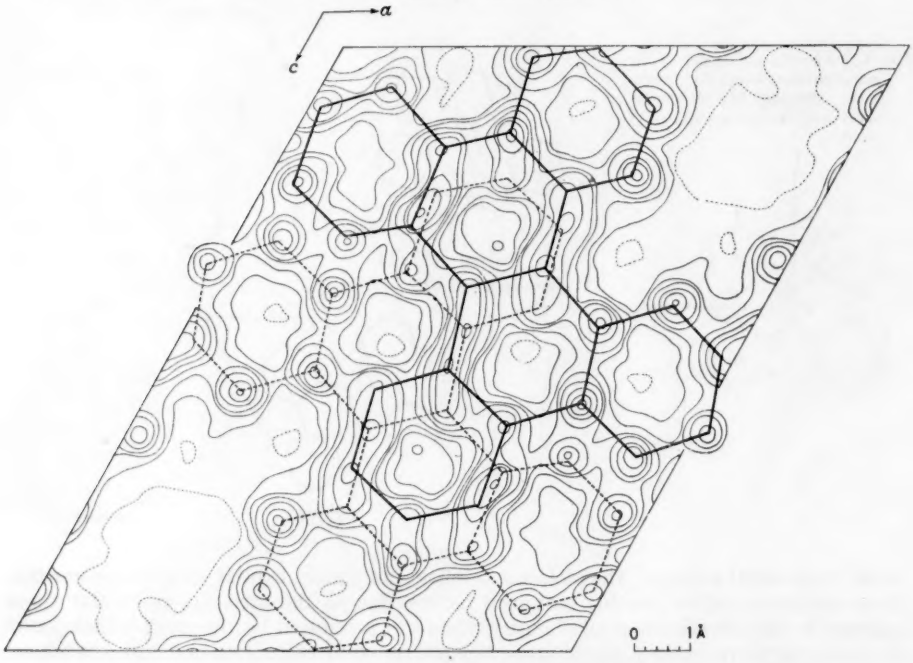
TABLE 2. *Experimentally-measured atomic co-ordinates (in* Å).

Atom *	x	z	Atom *	x	z	Atom *	x	z	Atom *	x	z
1	1·96	3·82	8	6·54	2·62	15	4·40	8·48	21	7·46	5·69
2	0·49	2·76	9	8·59	5·26	16	4·01	6·92	22	7·91	7·21
3	0·20	1·22	10	9·96	6·28	17	3·05	3·61	23	6·77	7·65
4	1·31	0·82	11	10·49	7·80	18	2·88	2·03	24	5·15	6·49
5	3·54	0·22	12	9·43	8·28	19	3·91	1·75	25	4·68	4·87
6	4·66	0·05	13	7·08	9·24	20	5·52	2·92	26	5·89	4·47
7	6·26	1·27	14	5·91	9·52						

* Cf. Fig. 1 and footnote, below.

An objective assessment of the accuracy of the u and w co-ordinates is not possible in view of their incomplete refinement; however, the mean shift after one refinement cycle was about 0·05 Å, and as it is probable that a single cycle would suffice to complete the refinement if the remaining signs were known, it is reasonable to estimate the mean errors in co-ordinates at about 0·05 Å.

FIG. 3. *The electron-density projection on* (010). *The contours are drawn at intervals of* 1 e.Å^{-2}, *with the one-electron contour dotted.*



The molecular dimensions measured from the projection on (010) are shown in Fig. 5: the projected bond lengths vary from 1·20 to 1·50 Å. The molecule is not centrosymmetric nor is the projection consistent with a molecular model in which the carbon atoms are arranged at the corners of regular hexagons. From the variations in the projected interatomic distances it can be deduced that the molecule as a whole is not planar, a conclusion supported by the increase in the distance between atoms 1 and 16 * from the value of 2·4 Å appropriate to a planar, regular model to a value, in projection, of 2·75 Å.

It is theoretically possible for a non-planar tetrabenzonaphthalene molecule to exist in

* In this paper the numbers used in references to the carbon atoms are those shown in Fig. 1 and not those strictly related to the name tetrabenzonaphthalene.

TABLE 3. *List of observed and calculated structure factors.*

h0l	Fo	Fc	*h0l*	Fo	Fc	*h0l*	Fo	Fc	*h0l*	Fo	Fc
200	88†	108	806	8	9	$\bar{6}04$	5	15	$\bar{1}4,12$	8	− 2*
4	65	60	7	0	− 1	5	0	0	13	3	− 8
6	53	−50	8	3	4	6	15	−22	14	7	− 8
8	14	2*	9	5	− 5	7	7	8	15	7	7
10	16	−18	10	5	1*	8	5	−12			
12	0	4				9	12	−13	$\bar{1}6,01$	13	5*
14	9	−11	10,01	9	9	10	3	− 1*	2	55	52
16	0	− 4	2	0	3	11	8	− 9	3	44	−51
18	0	1	3	0	3	12	19	14	4	7	−14
20	0	− 1	4	0	− 3	13	4	0*	5	6	− 1*
22	3	− 1*	5	4	6	14	0	2	6	0	−10
			6	0	3	15	3	5	7	0	− 4
001	70	−78	7	0	− 2				8	9	−10
2	14	−13	8	0	− 3	$\bar{8}01$	9	10	9	0	− 9
3	20	15	9	14	−12	2	10	7	10	11	− 8
4	10	11				3	37	−35	11	4	5
5	15	15	12,01	10	3*	4	59	43	12	10	−10
6	12	− 7	2	9	13	5	6	− 1*	13	6	− 5
7	3	− 3	3	0	4	6	4	0*	14	0	− 1
8	3	6	4	7	5	7	7	− 7	15	7	8
9	14	15	5	6	0*	8	8	12			
10	4	4	6	0	4	9	6	− 2*	$\bar{1}8,01$	7	4
11	0	− 4	7	0	− 4	10	0	5	2	0	− 3
12	0	0	8	10	5	11	0	2	3	33	−36
13	14	11				12	12	12	4	14	− 1*
			14,01	0	7				5	7	−10
201	83	83	2	8	− 2*	$\bar{1}0,01$	0	− 2	6	4	3
2	0	− 3	3	0	7	2	5	−13	7	13	11
3	16	−17	4	0	0	3	3	1*	8	19	−18
4	30	44	5	8	7	4	99	88	9	6	4
5	16	23				5	23	−19	10	0	1
6	13	11	16,01	3	4	6	7	14	11	0	− 3
7	19	18	2	4	− 3	7	12	11	12	6	− 5
8	26	26	3	0	3	8	0	− 1	13	5	− 4
9	7	3*	4	4	− 3	9	15	13	14	3	2
10	0	11				10	23	−25			
11	0	2				11	6	1*	$\bar{2}0,01$	0	1
12	14	−11	18,01	6	−10	12	0	3	2	7	2*
13	9	7	2	4	2	13	3	3	3	0	1
									4	6	−13
401	29	−27	$\bar{2}01$	70	−80	$\bar{1}\bar{2},01$	0	− 2	5	0	6
2	20	13	2	27	−24	2	13	13	6	0	4
3	0	1	3	20	20	3	0	− 7	7	0	− 5
4	17	−21	4	9	−14	4	8	11	8	10	−18
5	14	−13	5	71	71	5	13	1*	9	0	− 3
6	3	8	6	26	−19	6	16	−18	10	0	1
7	20	−16	7	17	20	7	0	− 1	11	0	5
8	28	25	8	6	− 5	8	8	6	12	0	− 1
9	20	17				9	10	12	13	0	1
10	0	2	$\bar{4}01$	37	28	10	6	4	14	3	− 8
11	7	1*	2	16	13	11	0	11			
			3	6	10	12	10	− 8			
601	48	−49	4	41	48	13	0	3	$\bar{2}\bar{2},01$	0	− 8
2	56	50	5	8	12	14	3	2	2	0	− 1
3	15	17	6	19	−15				3	0	− 2
4	0	0	7	28	−26	$\bar{1}4,01$	0	− 9	4	0	− 1
5	9	10	8	10	− 4*	2	6	11	5	0	− 1
6	0	− 5	9	8	− 5	3	3	− 5	6	0	1
7	6	14	10	8	6	4	0	0	7	3	−10
8	21	−16	11	4	2	5	3	− 4	8	0	− 3
			12	3	− 5	6	12	14	9	3	1*
801	86	−76	13	5	1*	7	0	5	10	0	1
2	21	11				8	7	13	11	0	0
3	7	0*	$\bar{6}01$	5	6	9	5	9	12	6	4
4	0	3	2	14	− 7*	10	4	3	13	0	− 3
5	13	− 9	3	24	21	11	27	−23	14	3	4

* Term omitted from Fourier summations. † Presumed secondary extinction error.

any of three stereoisomeric forms. There are two geometrical isomers (Fig. 6) differing in the relative inclinations of the four benzo-rings. The symmetries of idealised models of these isomers would be 222 and $\bar{1}$, of which the former can exist in two enantiomorphic forms. As the molecule is not centrosymmetric in projection its actual symmetry cannot be $\bar{1}$ and thus the stereoisomers encountered in the present work are probably those of symmetry 222. The crystals analysed here are centrosymmetric; thus the two enantiomorphs crystallise together and the crystals are those of the racemate. In this

FIG. 4. *The projection of the unit-cell contents on* (010).

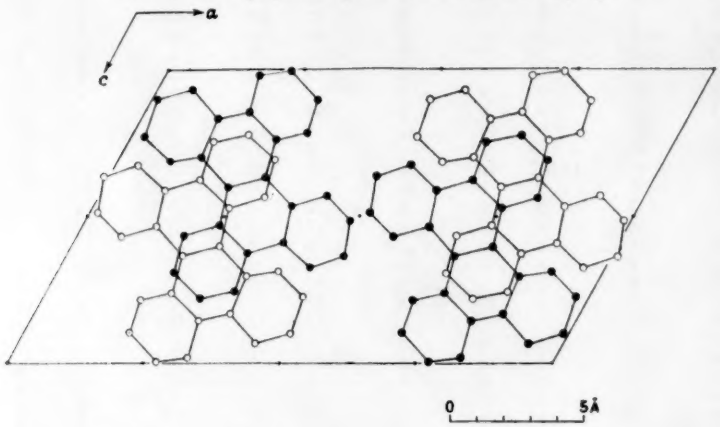


FIG. 5. *Projected bond lengths and intramolecular distances as determined from* ρ (*h*0*l*).

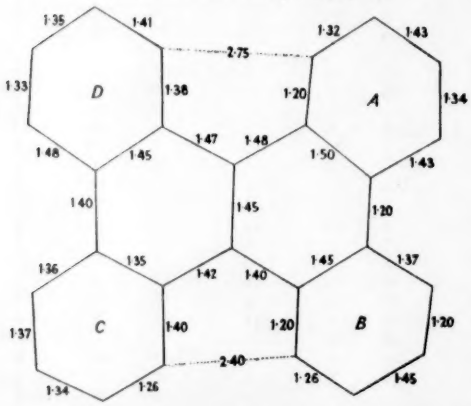
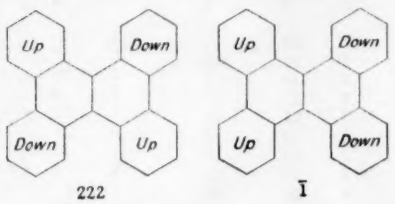


FIG. 6. *Possible configurations providing relief of intramolecular overcrowding.*



respect tetrabenzonaphthalene differs from 3 : 4-benzophenanthrene, where resolution of the optical isomers occurs on crystallisation.

The projection on (010) suggests that rings *A* and *B* are bent out of the mean molecular plane, while it follows from the suggested molecular symmetry that the bending must be in opposite directions. The necessity of relieving the overcrowding between atoms 1 and 16, and between 8 and 9, implies that ring *D* must be bent in the opposite sense to ring *A* and similarly for rings *B* and *C*; if these suggestions are correct the general mechanism of the relief of overcrowding in this molecule may well therefore be similar to that encountered in 3 : 4-benzophenanthrene (see Part III, *loc. cit.*). However, it has not been possible to obtain any further evidence from the projection on (010) about the exact nature of the distortions in the molecule.

The projected distance between atoms 1 and 16 has been increased to 2·75 Å, approaching the distances of 2·9—3·0 Å found between overcrowded carbon atoms in other molecules, and it thus appears not unlikely that the closest intramolecular approach distances in tetrabenzonaphthalene also lie within the above limits.

Experimental.—Good crystals of tetrabenzonaphthalene were grown by slow cooling of solutions in tetralin. The needle-shaped crystals are elongated along [010], showing {100}, {001}, and {20$\bar{1}$}.

The cell dimensions were determined from full-rotation and zero-level Weissenberg photographs taken about the [010] axis, the measurements of a and c being extrapolated to $\theta = 90°$ (Buerger, "*X*-Ray Crystallography," John Wiley and Sons, New York, 1942, Ch. 20). The crystallographic constants are: $a = 20{\cdot}45 \pm 0{\cdot}02$, $b = 7{\cdot}74 \pm 0{\cdot}02$, $c = 12{\cdot}18 \pm 0{\cdot}01$ Å; $\beta = 119° 33' \pm 7'$; d (found) = 1·292, d (calc.) = 1·275, $n = 4$. The space-group, determined from zero- and first-layer Weissenberg photographs about [010] and [001], is $P2_1/a$.

The intensities of the $h0l$ reflections were estimated visually from multiple-film Weissenberg photographs; the F^2 values were placed on an approximately absolute scale by Wilson's statistical method (*Nature*, **1942**, **150**, 152) and later rescaled by comparison with the calculated values.

We are grateful to Dr. D. Ginsburg for a sample of tetrabenzonaphthalene, to Mr. B. Smilovits for help with the calculations, and to Mr. R. Cohen, who has drawn the figures. This work was carried out during the tenure of the Porter scholarship of the University of Cape Town.

Laboratory of *X*-Ray Crystallography,
The Weizmann Institute of Science, Rehovoth, Israel. [*Received, January 11th*, 1954.]

Triazoles. Part III. Mono- and Di-methyl(phenyl)-1 : 2 : 4-triazoles.*

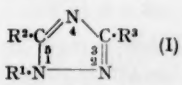
By M. R. Atkinson and J. B. Polya.

Reprint Order No. 5208.]

The structure of *N*-benzimidoyl-*N'*-methylhydrazine is established by its cyclization with ethyl chloroformate to 5-hydroxy-1-methyl-3-phenyl-1 : 2 : 4-triazole. Cyclization of this hydrazine with formic acid or acetic anhydride establishes the structures of the resulting 1-methyl-3-phenyl- and 1 : 5-dimethyl-3-phenyl-1 : 2 : 4-triazoles which differ from the isomeric 1-methyl-5-phenyl- and 1 : 3-dimethyl-5-phenyl-1 : 2 : 4-triazoles prepared from methylhydrazine and *N*-formylbenzamide or *N*-acetylbenzamide respectively. Methylation of 3-phenyl- and 3-methyl-5-phenyl-1 : 2 : 4-triazole by diazomethane affects mainly the "vicinal" nitrogen atom next to the phenyl group, but the other "vicinal" nitrogen atom is preferentially methylated if the sodiotriazoles are treated with methyl iodide. These observations may be correlated with the calculated π-electron densities on the nitrogen centres of 1 : 2 : 4-triazole and its anion.

The unsymmetrical Einhorn–Brunner reaction (Part I, *J.*, 1952, 3418):

$$R^1{\cdot}NH{\cdot}NH_2 + R^2{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}R^3 \longrightarrow$$



(I)

where $R^2 \neq R^3$ and $R^3{\cdot}CO_2H$ is a stronger acid than $R^2{\cdot}CO_2H$ occurs without the formation of the isomeric triazoles (I; with R^2 and R^3 interchanged) when R^1 = Me, R^2 = Ph, and R^3 = H or Me. The reaction between phenylhydrazine and *N*-acetylurethane, which affords 5-hydroxy-3-methyl-1-phenyl-1 : 2 : 4-triazole (I; R^1 = Ph, R^2 = OH, R^3 = Me), has been described before by Andreocci (*Gazzetta*, 1889, **19**, 448) and confirms the correlation between the orientation of the substituents R^2 and R^3 and the acidities of $R^2{\cdot}CO_2H$ and

* Part II, *J.*, 1954, 141.

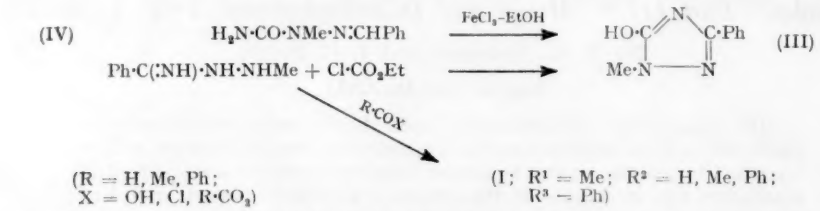
$R^3 \cdot CO_2H$. Andreocci's work has been repeated under more vigorous conditions but with the same results, confirming earlier observations (Parts I and II) which suggested that reaction times and temperatures do not affect the orientation of substituents.

Structural proofs of the new triazoles described in this paper are based on the unambiguous cyclization of substances containing the N·C·N·N skeleton, in particular amidrazones (II). The usual preparation of amidrazones from imidoates and hydrazines allows two possible structures (II*a* and *b*) :

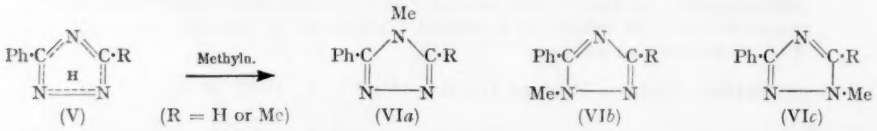
$$R' \cdot C(:NH) \cdot OEt + R'' \cdot NH \cdot NH_2 \begin{cases} \longrightarrow R' \cdot C(:NH) \cdot NH \cdot NHR'' & (IIa) \\ \longrightarrow R' \cdot C(:NH) \cdot NR'' \cdot NH_2 & (IIb) \end{cases}$$

The structure (II*a*) is commonly assumed (Jerchel and Fischer, *Annalen*, 1951, **574**, 85) although structure (II*b*) cannot be dismissed *a priori*, particularly when R″ = Me (cf. the condensation of methylhydrazine with potassium cyanate to $H_2N \cdot CO \cdot NMe \cdot NH_2$; von Brüning, *Annalen*, 1889, **253**, 5). Benzimidoylmethylhydrazine (II; R′ = Ph, R″ = Me), prepared from ethyl benzimidoate hydrochloride and methylhydrazine, when treated with ethyl chloroformate, afforded 5-hydroxy-1-methyl-3-phenyl-1 : 2 : 4-triazole (III) which is unambiguously available also from benzylidene-2-methylsemicarbazide (IV) (Young and Oates, *J.*, 1901, **79**, 659); this establishes the structure (II*a*) for the benzimidoylmethylhydrazine.

The triazoles obtained from benzimidoylmethylhydrazine by the action of benzoyl chloride, formic acid, and acetic anhydride are respectively 1-methyl-3 : 5-diphenyl-1 : 2 : 4-triazole (Part II) and the new compounds 1-methyl-3-phenyl- and 1 : 5-dimethyl-3-phenyl-1 : 2 : 4-triazole. The last two are not identical with the triazoles obtained from methylhydrazine sulphate and *N*-formyl- or *N*-acetyl-benzamide in Einhorn–Brunner reactions which must therefore afford 1-methyl-5-phenyl- and 1 : 3-dimethyl-5-phenyl-


(IV)
$H_2N \cdot CO \cdot NMe \cdot N{:}CHPh$
$FeCl_3$–EtOH
HO·C
C·Ph
(III)
$Ph \cdot C(:NH) \cdot NH \cdot NHMe + Cl \cdot CO_2Et$
Me·N
N
R·COX
(R = H, Me, Ph; X = OH, Cl, R·CO₂)
(I; R¹ = Me; R² = H, Me, Ph; R³ = Ph)

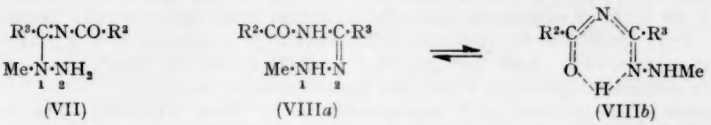
1 : 2 : 4-triazole respectively. Reference to the last-mentioned four compounds and their known 4-methyl isomers (Young and Oates, *loc. cit.*; Scheuing and Walach, G.P. 541,700, *Chem. Abs.*, 1932, **26**, 2469) permits the identification of the products obtained by the methylation of 3-phenyl- and 3-methyl-5-phenyl-1 : 2 : 4-triazoles (V) which, unlike the triazoles considered in Part II, could give three isomeric *N*-methyl derivatives (VI*a*, *b*, *c*) :



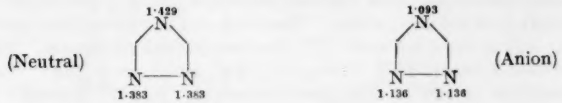
Methylations were carried out by causing diazomethane to react with the triazoles (V) in ether and by the action of methyl iodide on the sodium derivatives of the triazoles. The 4-methyl derivatives (VI*a*) have not been observed among the products, although our analytical methods (*e.g.*, comparison of products with artificial mixtures of known isomers) were adequate to detect these isomers in amounts above 3—5%. Diazomethane methylates mainly the " vicinal " nitrogen atom next to the phenyl group, giving (VI*b*), although the isomer (VI*c*) is formed in appreciable quantities. Thus 1-methyl-5-phenyl- and 1-methyl-3-phenyl-1 : 2 : 4-triazole are formed from 3-phenyl-1 : 2 : 4-triazole in the proportion 1·6 : 1, and 1 : 3-dimethyl-5-phenyl- and 1 : 5-dimethyl-3-phenyl-1 : 2 : 4-triazole from 3-methyl-5-phenyl-1 : 2 : 4-triazole in the proportion 3·7 : 1. The reaction between methyl

iodide and the sodiotriazoles favours the formation of (VI*c*), the proportions of (VI*c*) : (VI*b*) being 2 : 1 from 3-phenyl-1 : 2 : 4-triazole; 3-methyl-5-phenyl-1 : 2 : 4-triazole affords only the isomer (VI*c*) by this method.

The orientation rule observed in the reactions of phenylhydrazine with unsymmetrical diacylamines is consistent with the view that the most nucleophilic centre of the hydrazine ($N_{(2)}$) attacks the more electrophilic carbon centre of the CO·N·CO group in the diacylamine to initiate the reaction. In the case of methylhydrazine one might expect the primary attack to occur from $N_{(1)}$ except that in this case the resulting intermediate (VII) would be less stable than the alternative (VIII*a–b*) which would lead to cyclized products that have been found:



The annexed calculated values of π-electron densities at the nitrogen centres of the neutral molecule and anion of 1 : 2 : 4-triazole (R. D. Brown and I. M. Bassett, personal communication; cf. Orgell, Cottrell, and Dick, *Trans. Faraday Soc.*, **1951**, **47**, 113) may explain the observed trends of *N*-methylation as reported in this paper and Part II. In the neutral molecule the electron density is lowest, and so the acidity highest, on $N_{(1)}$ and $N_{(2)}$; these are the centres attacked by diazomethane and diazoethane. Methylation by the action of methyl iodide on sodiotriazoles involves the triazole anion in which $N_{(1)}$ and $N_{(2)}$, the more nucleophilic centres, are attacked in preference to $N_{(4)}$. Unsymmetrical



C-substitution of 1 : 2 : 4-triazole by methyl and/or phenyl does not reverse the relative order of π-electron densities on the " vicinal " nitrogen atoms compared with that on $N_{(4)}$ but the π-electron densities of $N_{(1)}$ and $N_{(2)}$ become different. Preferential methylation of neutral (V) to (VI*b*) by diazomethane indicates the reduction of π-electron density on the " vicinal " nitrogen atom nearest to the phenyl group and an increase on that nearest to the methyl group. The same conclusions may be reached on considering the course of the methylation of sodiotriazoles by methyl iodide. The opposite effects of *C*-phenyl and *C*-methyl groups on the π-electron densities of the neighbouring " vicinal " nitrogen atoms account for the greater disparity of the proportion (VI*b*) : (VI*c*) when 3-methyl-5-phenyl-1 : 2 : 4-triazole is methylated by either method.

Experimental

M. p.s are corrected. Extracts in organic solvents were dried with sodium sulphate.

N-Benzimidoyl-N′-methylhydrazine.—Methylhydrazine was prepared from its sulphate (57·6 g.) and powdered potassium hydroxide (100 g.) in water (50 c.c.). The mixture was distilled until the distillate no longer reduced Fehling's solution. After saturation of the distillate with potassium hydroxide methylhydrazine was separated and boiled under reflux with barium oxide (10 g.) in dry nitrogen for 12 hr. On distillation in nitrogen, anhydrous methylhydrazine (9·2 g., 50%), b. p. 87°/760 mm., was obtained. Further (moist) material could be obtained from the alkaline residues.

Methylhydrazine (4·6 g.) was added to a mixture of ethyl benzimidoate hydrochloride (18·5 g.) and dry pyridine (40 c.c.), with cooling by water. After 0·5 hr. the crystalline mass was filtered off and washed with dry ether (3 × 20 c.c.). *N*-Benzimidoyl-*N′*-methylhydrazine hydrochloride (12·6 g., 68%) was obtained as colourless prisms, m. p. 185° (cf. Jerchel and Fischer, *loc. cit.*). On combination of the pyridine and ether filtrates more of the same material (3·3 g., 18%),

m. p. 185°, was precipitated. The hydrochloride (11·1 g.) was dissolved in 10% aqueous sodium carbonate (50 c.c.), and the solution extracted with chloroform (4 × 50 c.c.). Removal of the solvent below 30° left N-*benzimidoyl*-N′-*methylhydrazine* (7·0 g., 78% calc. on the hydrochloride) as a colourless oil which decomposed during several hours and more rapidly on heating. This material was used without further purification. When a chloroform solution of the base was shaken with aqueous cobalt chloride (<5 parts per million of Co) a purple colour developed in the organic phase.

N-Benzimidoyl-*N*′-methylhydrazine hydrochloride (3·7 g.) was converted into the free base and immediately treated with ethyl chloroformate (3 c.c.) (cooling) and the mixture was then heated for 10 min. on a steam-bath. Removal of excess of solvent at 20 mm. left a colourless, fibrous solid which was neutralized with 10% aqueous sodium carbonate and extracted with ether (4 × 30 c.c.). Evaporation and crystallization from benzene–light petroleum (b. p. 60—80°; 1 : 1) gave 5-hydroxy-1-methyl-3-phenyl-1 : 2 : 4-triazole (1·9 g., 54%) (Found : C, 61·8; H, 5·1; N, 24·2. Calc. for $C_9H_9ON_3$: C, 61·7; H, 5·2; N, 24·0%), m. p. 219° alone or mixed with material prepared by Young and Oates's method (*loc. cit.*).

Cyclization of N-*Benzimidoyl*-N′-*methylhydrazine to Basic Triazoles.*—The benzimidoylhydrazine hydrochloride (3·7 g.) and formic acid (99—100%; 4·6 g.) were mixed at room temperature and after 0·5 hr. were boiled under reflux for 1 hr. Completion of the reaction was ascertained by testing for amidrazone with cobalt chloride. The product was poured into 10% aqueous sodium carbonate (50 c.c.) and extracted with chloroform (3 × 50 c.c.). Distillation of the residue obtained from the chloroform extract gave 1-*methyl*-3-*phenyl*-1 : 2 : 4-*triazole* (2·2 g., 69%), prisms, m. p. 23°, b. p. 110°/1 mm. (Found : C, 68·3; H, 6·1; N, 26·2. $C_9H_9N_3$ requires C, 67·9; H, 5·7; N, 26·4%). The triazole was evaporated with a chloroform solution of picric acid and the residue recrystallized from ethanol, giving the *picrate*, yellow needles, m. p. 183° (Found : C, 46·4; H, 3·1; O, 28·8. $C_{15}H_{12}O_7N_6$ requires C, 46·4; H, 3·1; O, 28·8%). The same triazole was obtained in inferior yield by using free benzimidoylmethylhydrazine.

Benzimidoylmethylhydrazine [from the hydrochloride (3·7 g.)] and acetic anhydride (3 c.c.) were mixed and initially cooled with water. Reaction was completed during 0·5 hr. on a steam-bath. The product was neutralized with 10% aqueous sodium carbonate. Isolation by chloroform gave 1 : 5-*dimethyl*-3-*phenyl*-1 : 2 : 4-*triazole* (2·0 g., 58%), m. p. 113°. Crystallisation from benzene and sublimation at 120°/2 mm. gave prisms, m. p. 117° (Found : C, 69·6; H, 6·2; N, 24·6. $C_{10}H_{11}N_3$ requires C, 69·3; H, 6·4; N, 24·3%). The *picrate* crystallized from ethanol as yellow silky needles, m. p. 166° (Found : C, 48·1; H, 3·7. $C_{16}H_{14}O_7N_6$ requires C, 47·7; H, 3·5%).

Benzimidoylmethylhydrazine hydrochloride (0·5 g.) and benzoyl chloride (3 c.c.) were heated together at 120° for 12 hr. The resulting clear solution was poured into 10% aqueous sodium carbonate and extracted with chloroform (3 × 50 c.c.). Removal of the solvent left 1-methyl-3 : 5-diphenyl-1 : 2 : 4-triazole (0·6 g., 94%), m. p. 80°; crystallization from benzene–light petroleum (b. p. 60—80°) gave colourless prisms, m. p. 84° alone or mixed with authentic material (Part II). The substance was characterized further as the picrate, m. p. and mixed m. p. 135°.

Einhorn–Brunner Reactions.—Urethane (66 g.), acetic anhydride (204 g.), and acetyl chloride (1 c.c.) were boiled under reflux for 1 hr. and the product was distilled. *N*-Acetylurethane (80·5 g., 83%), b. p. 105—106°/18 mm., m. p. 78°, was collected (cf. McCreath, *Ber.*, 1875, **8**, 1181). Acetylurethane (11·8 g.) and phenylhydrazine hydrochloride (11·8 g.) were kept at 150—160° for 12 hr. The product was neutralized with 10% aqueous sodium carbonate and extracted with ether (3 × 50 c.c.). 5-Hydroxy-3-methyl-1-phenyl-1 : 2 : 4-triazole (4·3 g., 30%), m. p. 167° (cf. Andreocci, *loc. cit.*), was obtained on evaporation of the extract. Sublimation and recrystallization from ethyl acetate did not raise the m. p.

N-Formylbenzamide (m. p. 112°; 7·5 g.) and methyl hydrazine sulphate (7·2 g.) were kept at 120° for 4 hr. The clear liquid was neutralized with 10% aqueous sodium carbonate and extracted with chloroform (3 × 50 c.c.). Evaporation of the extract left 1-*methyl*-5-*phenyl*-1 : 2 : 4-*triazole* (5·0 g., 63%), m. p. 57—58°. Crystallization from benzene–light petroleum (b. p. 60—80°) and sublimation at 60°/2 mm. gave colourless prisms, m. p. 59° (Found : C, 67·8; H, 5·6; N, 26·5. $C_9H_9N_3$ requires C, 67·9; H, 5·7; N, 26·4%). The *picrate* crystallized from ethanol as flat yellow needles, m. p. 178° (Found : C, 47·0; H, 3·3. $C_{15}H_{12}O_7N_6$ requires C, 46·4; H, 3·1%). This triazole and its picrate depressed the m. p.s of 1-methyl-3-phenyl-1 : 2 : 4-triazole and its picrate respectively.

N-Acetylbenzamide (m. p. 116°, 6·1 g.) and methylhydrazine sulphate (3·6 g.) were caused to react at 160° for 6 hr. and the product was isolated as in the preceding experiment. After

chromatography in benzene on alumina 1 : 3-*dimethyl*-5-*phenyl*-1 : 2 : 4-*triazole* (2·6 g., 65%), m. p. 66—68°, was obtained. Crystallization from benzene–light petroleum (b. p. 60—80°) and sublimation at 60°/2 mm. gave colourless prisms, m. p. 72° (Found : C, 70·0; H, 6·4; N, 24·1. $C_{10}H_{11}N_3$ requires C, 69·3; H, 6·4; N, 24·3%). The *picrate* crystallized from methanol as yellow prismatic needles, m. p. 172° (Found : C, 48·3; H, 3·5; O, 27·3. $C_{16}H_{14}O_7N_6$ requires C, 47·7; H, 3·5; O, 27·8%). The triazole and its picrate depress the m. p.s of 1 : 5-dimethyl-3-phenyl-1 : 2 : 4-triazole and its picrate respectively. The same triazole was obtained in low yield together with much benzamide when the reactants were heated in an acetic acid–sodium acetate buffer (pH 5) for 10 hr.

N-Formylbenzamide (0·55 g.) and semicarbazide hydrochloride (0·42 g.) were kept at 160° for 1 hr. Water (5 c.c.) was added and the mixture was neutralized with solid sodium carbonate. Filtration removed hydrazodicarboxyamide (0·125 g., 29%), m. p. 257° (decomp.). The filtrate was extracted with ether (2 × 50 c.c.) and on evaporation left colourless needles, m. p. 114—115°. Sublimation at 140°/1 mm. gave 3-phenyl-1 : 2 : 4-triazole (0·16 g., 30%), m. p. 118°. This material did not depress the m. p. of 3-phenyl-1 : 2 : 4-triazole, m. p. 119°, prepared according to Hoggarth (*J.*, 1949, 1160), who reports m. p. 121°.

N-Acetylbenzamide (8·2 g.) and semicarbazide hydrochloride (5·6 g.) were caused to react and the products isolated as in the preceding experiment. Hydrazodicarboxyamide (1·2 g., 21%), m. p. 257°, was obtained together with 3-methyl-5-phenyl-1 : 2 : 4-triazole (1·4 g., 18%), m. p. 166° after sublimation at 140°/1 mm. (Heller, *J. pr. Chem.*, 1929, **120**, 49, reports 164·5°) (Found : C, 68·4; H, 5·8. Calc. for $C_9H_9N_3$: C, 67·9; H, 5·7%). Benzamide (121 g.) and acetylhydrazine (74 g.) were mixed and heated in a metal-bath. The internal temperature was raised from 210° to 260° during 12 hr. Water, ammonia, and benzonitrile distilled through a short column. The melt was poured into 5N-hydrochloric acid (500 c.c.). After being heated to boiling, the liquid was cooled and 3 : 5-diphenyl-1 : 2 : 4-triazole (62 g.), m. p. and mixed m. p. 189—191°, was filtered off. The filtrate was partially neutralized with concentrated aqueous ammonia and neutralization was completed with 10% aqueous sodium carbonate. Extraction with benzene (400 c.c.) and removal of the solvent gave a mixture of oil and crystals. The latter were recrystallised from benzene–light petroleum (b. p. 100—120°), giving 3-methyl-5-phenyl-1 : 2 : 4-triazole (21·3 g., 13%), m. p. 165° (from toluene) alone or mixed with material obtained by the Einhorn–Brunner reaction. This was further characterised as the picrate, m. p. 158° (from methanol) (cf. Heller). The same material was prepared from acetamide (18 g.) and benzoylhydrazine (41·5 g.) by Heller's method which afforded 14·4 g. of the substance, m. p. 160—164°; further purification of this material was difficult.

Methylation of 3-*Phenyl*-1 : 2 : 4-*triazole*.—3-Phenyl-1 : 2 4-triazole (2·9 g.) was added to a solution of sodium (0·46 g.) in methanol (10 c.c.). Methyl iodide (2·8 g.) was added and the reactants were kept in a sealed tube for 1 hr. at 20° and 12 hr. at 100°. Methanol was removed by distillation and the residual oil poured into 20% aqueous sodium hydroxide (50 c.c.). Extraction with ether afforded a pale oil (2·9 g.) which was fractionated through a vacuum-jacketed Vigreux column. The fraction of b. p. 114—116°/2—3 mm. had m. p. 55—57° (0·89 g., 28%); after sublimation at 60°/2 mm. it had m. p. 58° and mixed m. p. with 1-methyl-5-phenyl-1 : 2 : 4-triazole 59°. The picrate had m. p. and mixed m. p. 178° (from ethanol). An intermediate fraction (0·1 g.) having been discarded, the fraction of b. p. 120—122°/2—3 mm. (1·79 g., 56%) was collected and sublimed on to a condenser cooled with liquid air. 1-Methyl-3-phenyl-1 : 2 : 4-triazole was obtained as colourless prisms, m. p. and mixed m. p. 23°; its picrate, recrystallized from ethanol, had m. p. 181° and mixed m. p. 181—182°.

3-Phenyl-1 : 2 : 4-triazole (1·45 g.) in dry methanol (10 c.c.) was treated with 3 portions of ethereal diazomethane [generated from 10 g. (total) of nitrosomethylurea] at 2-day intervals. After removal of the solvent the residual oil was fractionated as before, giving 1-methyl-5-phenyl-1 : 2 : 4-triazole (0·89 g., 56%), m. p. 52—55° (picrate, m. p. and mixed m. p. 178°), and 1-methyl-3-phenyl-1 : 2 : 4-triazole (0·54 g., 34%), m. p. 18—20° (picrate, m. p. and mixed m. p. 181—182°).

Methylation of 3-*Methyl*-5-*phenyl*-1 : 2 : 4-*triazole*.—This triazole (7·9 g.) was suspended in a solution of sodium (1·65 g.) in dry methanol (30 c.c.). Methyl iodide (7·1 g.) was added and the reaction was carried out as before. Fractionation under reduced pressure gave a material, b. p. 116—118°/2—3 mm. (8·1 g.), m. p. 111—114°. Recrystallization from benzene–light petroleum (b. p. 60—80°) gave 1 : 5-dimethyl-3-phenyl-1 : 2 : 4-triazole (7·8 g., 90%), m. p. and mixed m. p. 117°. The crude product before distillation gave a picrate, m. p. 164°, which crystallized from ethanol as yellow needles with m. p. and mixed m. p. 166°.

3-Methyl-5-phenyl-1 : 2 : 4-triazole (7·9 g.) in dry methanol (50 c.c.) was treated with diazo-

methane (from 15 g. of nitrosomethylurea), and the products were isolated as before. The fraction with b. p. 93—96°/1 mm. crystallized and was rubbed with benzene–light petroleum (1 c.c.). This material (3·2 g., 37%) had m. p. and mixed m. p. 70—72° with 1 : 3-dimethyl-5-phenyl-1 : 2 : 4-triazole; the picrate had m. p. and mixed m. p. 170—171°. After discarding of an intermediate fraction (0·15 g.), material with b. p. 105—110°/1 mm. was collected and allowed to solidify. After being washed with benzene–light petroleum (1 c.c.) the substance (0·9 g., 10%) had m. p. and mixed m. p. 113—115° with 1 : 3-dimethyl-5-phenyl-1 : 2 : 4-triazole; the picrate, crystallized from ethanol, had m. p. and mixed m. p. 166°.

The authors acknowledge with thanks an I.C.I.A.N.Z. Research Fellowship (to M. R. A.) and thank Dr. R. D. Brown and Mr. I. M. Bassett of the University of Melbourne who permitted the use of their calculations. Dr. R. D. Brown has also assisted with discussion and advice. The analyses were carried out by the Microanalytical Laboratory of the C.S.I.R.O., Melbourne, under the direction of Dr. K. W. Zimmmermann.

UNIVERSITY OF TASMANIA, HOBART. [*Received, March 15th,* 1954.]

The Oxides of Uranium. Part IV. The System* UO_2–ThO_2–O.

By J. S. ANDERSON, D. N. EDGINGTON, L. E. J. ROBERTS, and (in part) E. WAIT.

[Reprint Order No. 5301.]

Several mixed crystals having the general formula $U_xTh_{1-x}O_2$ were oxidised at temperatures of 100—1000°. Oxidation under appropriate conditions yielded cubic phases; no other structures were formed when $x < 0{\cdot}5$. The densities of the cubic oxidised phases showed that oxygen entered interstitial positions in the original lattice. When $x > 0{\cdot}5$, the amount of interstitial oxygen that could be accommodated was limited to 1·4 atoms per unit cell. When $x < 0{\cdot}5$, the concentration of interstitial oxygen came to a reversible equilibrium with the ambient oxygen pressure at high temperatures. The unit cell contracted as the average uranium valency increased from 4·0 to 5·0 and began to expand as the uranium valency increased from 5·0 to 5·5. This result indicates that isolated uranium cations with more than 5 positive charges cannot exist in these crystals.

URANIUM DIOXIDE is capable of absorbing oxygen at low temperatures, the extra oxygen entering interstitial positions in the fluorite lattice (Anderson and Alberman, *J.*, 1949, S 303; Anderson *et al.*, unpublished work). The nonstoicheiometric oxides so formed are metastable and split up on high-temperature vacuum annealing to UO_2, U_3O_8, and a cubic oxide U_4O_9 which probably contains one interstitial oxygen atom in every unit cell of the original dioxide lattice; all the oxides form U_3O_8 when heated in oxygen at high enough temperatures for this phase to be nucleated. The extension of this work to include the oxidation of uranium dioxide–thorium dioxide mixed crystals has enabled the study of interstitial anions in the fluorite lattice to be carried further, since at some compositions fluorite phases with extra oxygen in interstitial positions are stable over a wide range of temperature and oxygen content.

Hund and Niessen (*Z. Elektrochem.*, 1952, **56**, 972) prepared a series of oxide mixed crystals by heating mixtures of thorium and uranyl nitrates in air and annealing the products in air at 1200°, and found that a fluorite phase extended from 0 to 56·5 moles % of uranium oxide. The oxygen content of these preparations was not determined. On the basis of density measurements they postulated that anomalous mixed crystals containing an intact cation sub-lattice and interstitial oxygen occurred above 50 moles % of UO_n and possibly below 15 moles % of UO_n, but that at intermediate uranium concentrations the anion sub-lattice was intact and the extra oxygen was accommodated by the occurrence of cation vacancies.

In this study, we started always with fully reduced specimens of uranium dioxide–thorium dioxide mixed crystals, containing a normal fluorite anion sub-lattice, with U^{4+}

* Part III, *J.*, 1953, 1731.

and Th^{4+} randomly distributed over the cation positions. The additional oxygen in the oxidised phases was measured during their preparation or determined by analysis. The structure and density could then be determined as a function of oxygen content for each mixed crystal. We have found no evidence that any types of defects other than interstitial anions are introduced into any of the fluorite phases in the course of oxidation. It was possible to determine the composition limits of the fluorite phases and the effect on the size of the unit cell of introducing interstitial oxygen. Structures other than fluorite were formed by complete oxidation of the uranium-rich mixed crystals.

Experimental

Preparation.—The starting materials were solutions of "AnalaR" uranyl nitrate and "AnalaR" thorium nitrate, analysed gravimetrically. Uranium was weighed as U_3O_8 after precipitation with ammonia solution, and thorium as ThO_2 after precipitation as oxalate or sebacate. Aliquot portions of these solutions were mixed and run slowly into an excess of ammonia solution with vigorous stirring. The precipitating conditions were those used by Trzebiatowski and Selwood (*J. Amer. Chem. Soc.*, 1950, **72**, 4504), except that ammonium nitrate was not added when a fine particle product was desired, especially at the higher uranium concentrations. The precipitates were centrifuged, washed, and dried at 120°. The highly coloured, glassy products were ground, ignited in air at 450—600°, and reduced with hydrogen or carbon monoxide at 900—1400°; carbon monoxide was preferred because of the danger of hydrogen chemisorption (L. E. J. Roberts, unpublished work). For the reduction, the samples were placed in alumina boats inside a Mullite tube which was heated by a radiation furnace. The gases were purified by passage over hot palladium–asbestos or hot copper and through potassium hydroxide or magnesium perchlorate. The oxides were cooled in the flowing gas and their homogeneity was proved by *X*-ray examination. The apparent cell edge was an accurate linear function of composition, in agreement with Slowinski and Elliott's data (*Acta Cryst.*, 1952, **5**, 768).

In order to obtain very well crystallised samples for *X*-ray work, samples of the mixed crystals were pelleted and heated in dynamic vacuum in thoria crucibles to 1700—2100°; such treatment also sufficed for the original reduction. The vacuum furnace was described by Alberman (*J. Sci. Instr.*, 1950, **27**, 280). The sintered pellets were broken in an iron percussion mortar and finely ground in an agate mortar. Although crystallinity was improved, the high-temperature annealing produced no significant change in the cell-size of homogeneous products. Homogeneous products were usually, but not always, obtained by the gaseous reduction method; they were always obtained after high-temperature annealing.

The only major impurity found was cerium, present to the extent of 0·4% * in the thorium nitrate. The colours of the mixed crystals changed from uranium dioxide-brown at high uranium concentrations to a "uranous" green at 25 moles % of uranium dioxide; the green colour became progressively lighter as the U^{4+} ions were further diluted with Th^{4+}.

X-Ray Measurements.—Samples were exposed in 0·3-mm. thin-walled Pyrex capillaries in 9-cm. or 19-cm. Unicam cameras. Cu-$K\alpha$ radiation was used with a nickel filter; $\lambda\alpha_1$ was assumed to be 1·537396 k.X.U., and $\lambda\alpha_2$ 1·541232 k.X.U. Values of a_{100} at $\theta = 90°$ were found by extrapolation from a values calculated above $\theta \sim 50°$, Nelson and Riley's method (*Proc. Phys. Soc.*, 1945, **57**, 160) being used. Values of a_{103} could be obtained accurate to $\pm$0·0003 k.X.U. from 19-cm. photographs of well-crystallised samples, and to $\pm$0·001 k.X.U. from good 9-cm. photographs. Poorly crystalline phases gave photographs with no resolution of the $K\alpha_1$–α_2 doublets, and the a_{100} values were accurate to only $\pm$0·003 k.X.U.

Density Measurements.—These were carried out by using either helium or toluene as the displaced fluid. The densities in helium were measured after outgassing at 200—300° and were reproducible to within $\pm$0·3%. The densities in toluene were measured by weighing small, open glass bulbs containing the powders first in air and then in toluene, the liquid being admitted after evacuation at 100—150°, flushing with toluene vapour at room temperature and again outgassing; corrections were made for the weight and buoyancy of the empty bulbs. This method seems more accurate than the usual pycnometric method when the quantities of solid available are small. With 3 g. (0·3 c.c.) samples, the densities were reproducible to $\pm$0·3%. The two methods, when directly compared on the same samples, yielded results in agreement to $\pm$0·3%.

Oxidation Measurements and Analysis.—The oxygen absorbed by the reduced phases by

* We are indebted to the Spectrographic Group at A.E.R.E. for this analysis.

oxidation at 100—900° was estimated by gain of weight and by gas-volumetric methods. The gas measurements were the more accurate because the relative increase in weight was small. For the gas measurements, a sample was weighed into a small Vitreosil U-tube, which was connected through capillary lines to a U-tube mercury manometer, of which one limb was a gas burette; the apparatus could be evacuated through a conventional high-vacuum system. The sample could be heated by a small furnace. The dead spaces in the leads and bulbs were determined with helium. B.O.C. " Spectroscopically Pure " oxygen was used for the oxidation experiments without further purification. Preparations which could have oxidised appreciably in air at room temperature (Part V, following paper) were reduced with carbon monoxide at 600—800° and pumped at 800° immediately before the oxidation experiment.

Some oxidations were carried out at 120 atm. pressure. The samples were placed in open silica tubes inside a stainless-steel tube ($\frac{1}{2}$" o.d., $\frac{1}{4}$" i.d.), which was connected through high-pressure lines and valves to a B.O.C. gauge and an oxygen cylinder. The mixture of nitrogen dioxide and oxygen obtained by heating lead nitrate *in vacuo* was used as the oxidising gas in a few experiments, as had been done by Katz and Gruen (*J. Amer. Chem. Soc.*, **1949**, **71**, **2106**) in a study of the oxidation of UO_2, U_3O_8, and NpO_2. In our experiments the oxidising gas was circulated at about 1 atm. pressure over the previously outgassed sample by means of a thermal-gradient pump.

The products of such oxidations, and some other samples, were analysed for oxygen in excess of $MO_{2\cdot00}$ by reduction with carbon monoxide and measurement of the carbon dioxide produced. The oxidised samples were evacuated at temperatures below 200°, when no oxygen was lost, and heated to 800° in a closed system, any oxygen evolved being measured and then pumped off after isolation of the sample. When measurable pressures of oxygen were no longer generated the sample was cooled, pure carbon monoxide was admitted, and the sample heated again to 800°. Carbon monoxide was streamed over the sample until no more dioxide could be frozen out of the issuing gas in a liquid-oxygen trap. The carbon dioxide collected was expanded into a known volume, and the pressure and temperature were measured. The oxygen content of the original sample was then calculated as (vol. of oxygen + 0·5 vol. of carbon dioxide) found, and the sample was recovered in the fully reduced state and could be used again. The results of gas-volumetric measurements of oxygen absorbed and of analyses by the above method were in good agreement. Results on gain of weight were also in general agreement when allowance was made for their lower accuracy.

Results and Discussion

Structure of the Oxidised Phases.—Mixed crystals of all compositions—even those containing only 1% of uranium dioxide—oxidised rapidly at temperatures below 400°. The preparative conditions, analyses, and *X*-ray characteristics of many of the oxidised phases are collected in Table 1. Where the conditions of oxidation are not quoted, the sample was oxidised in 5—15 cm. of oxygen, or in air. Many of the products were annealed in sealed, evacuated tubes. The compositions are expressed both as the additional oxygen atoms per " molecule " of mixed crystal and as the average valency reached by the uranium. Preparations referred to as " C.C." were crushed crystals, formed by high-temperature annealing and pulverising; the others were the products of reduction in carbon monoxide or hydrogen. The cell-edge measurements in Table 1 refer to f.c.c., fluorite, phases.

The oxidised phases were always cubic fluorite phases when the temperature of oxidation was lower than 200°. At higher temperatures, mixed crystals containing more than 80 moles % of uranium dioxide formed other structures, and finally a U_3O_8-like structure. The fluorite oxidised phases of mixed crystals containing less than 78 moles % of dioxide were stable in air at all temperatures up to 1400°, though oxidation in high-pressure oxygen broke the cubic structure of the mixed crystal containing 66 moles % of uranium dioxide. Oxidation under any conditions of mixed crystals containing less than 50 moles % of uranium dioxide yielded only fluorite phases. These results differ from those reported by Hund and Niessen (*loc. cit.*), who found U_3O_8 and a limiting fluorite phase after roasting in air samples with more than 56·5 moles % of dioxide. The discrepancy is probably due to the different methods of preparation. Hund and Niessen prepared the oxidised phases directly from hydroxides containing sexavalent uranium; the nucleation of U_3O_8 might have been facilitated by this procedure.

A small particle-size preparation of $U_{0\cdot90}Th_{0\cdot10}O_2$ was oxidised at temperatures below 200° to give cubic phases; the *X*-ray lines tended to broaden in the direction caused by a cell contraction, in a manner strongly reminiscent of the behaviour of uranium dioxide

TABLE 1. *Preparation, analyses, and structures of* $U_xTh_{1-x}O_{2+y}$.

		Valency	Details of oxidation		*X*-Ray results	
x	*y*	of U	Treatment	Temp.	a_{100}, k.X.U.	Remarks
0·90	0	4·0	—	—	5·468	
	0·21	4·47	Oxidised	155°	5·459	Broad lines
			Annealed	400	5·443	
	0·30	4·67	Oxidised	150	—	
			Annealed	400	5·444	
	0·35	4·79	Oxidised	140	5·441	
			Annealed	500	—	Lines split
0·90	0	4·0	—	—	5·471	
(C.C.)	0·14	4·31	Oxidised	340	—	
			Annealed	800	5·454	
	0·31	4·68	Oxidised	440	5·443	
			Annealed	800	5·443	
	0·25	4·55	Oxidised	305	5·471	
					5·442	
			Annealed	590	5·448	
	0·35	4·77	Oxidised	270	5·441	
					5·474	— Faint
	0·39	4·87	Oxidised	350	5·442	+ Phase B
	0·40	4·89	Oxidised	305	5·442	+ Phase B
	0·44	4·97	Oxidised	450	5·442	+ Phase B
			Annealed	500	5·443	+ Phase B
			Annealed	700	5·446	+ Phase B
	0·63	5·39	Oxidised	600	—	(Orthorhombic)
0·82	0	4·0	—	—	5·480	
	0·14	4·35	Oxidised	130	5·472	
			Annealed	700	5·459	
	0·32	4·79	Oxidised	150	—	
				185	5·449	
			Annealed	450	5·455	
	0·53	5·29	Oxidation	600	—	(Orthorhombic)
0·78	0	4·0	—	—	5·485	
(C.C.)	0·33	4·85	Oxidation	900	—	
			Annealed	900	5·457	
	—	—	Oxidation	1400	5·453	
0·76	0	4·0	—	—	5·499	
(C.C.)	0·051	4·13	Oxidation	275		Broad lines
			Annealed	310	5·499	
					5·481	
			Annealed	700	5·488	
	0·17	4·46	Oxidised	300	5·499	
					5·478	
	0·34	4·88	Oxidised	650	5·476	
			Annealed	310	5·477	
0·66	0	4·0	—	—	5·501	
(C.C.)	0·34	5·07	Oxidised	500	5·479	
	0·47	5·43	Oxid. 100 atm. O_2	550	—	(Low symmetry)
0·50	0	4·0	—	—	5·524	
	0·31	5·26	Oxid. 100 atm. O_2	500	5·510	
0·38	0	4·0	—	—	5·536	
	0·16	4·83	Oxidised	420	5·537	
					5·523	
	0·13	4·68	Oxidised	700	—	
			Annealed	800	5·527	
0·24	0	4·0	—	—	5·556	
	0·081	4·67	Oxidised	360	5·555	
					5·548	
			Annealed	400	5·549	
			Annealed	800	5·550	

(J. S. Anderson, to be published). The oxidation stopped at a composition $MO_{2\cdot35}$; rise of temperature by 20° caused no further oxidation. This product was poorly crystalline but apparently cubic, the cell edge having contracted from $a = 5\cdot466$ to 5·441 k.X.U. When this product was annealed at 400° *in vacuo*, the cube lines tended to split and a phase of lower symmetry was formed, which has not yet been fully investigated. The loss of cubic

symmetry implies an ordering of the previously randomly arranged additional oxygen in the fluorite lattice, and is analogous to the formation of tetragonal phases with compositions between $UO_{2\cdot30}$ and $UO_{2\cdot39}$ in the uranium oxide system. Oxidation above 200° to compositions below $MO_{2\cdot30}$ gave a two-phase product, one being the unoxidised material and the other a cubic phase with $a = 5\cdot442$ k.X.U. Oxidation beyond $MO_{2\cdot35}$ caused the appearance of a few lines of a new phase (denoted " phase B " in Table 1) which could be indexed fairly satisfactorily on the basis of a simple cubic cell having $a = 7\cdot45$ k.X.U., and the fluorite phase with $a = 5\cdot442$ k.X.U. persisted. As oxidation proceeded, the lines of " phase B " became stronger relative to the cubic phase. The composition of " phase B " has not yet been established, but it seems fair to conclude from the results in Table 1 that the fluorite phase with $a = 5\cdot442$, stable at high temperatures, had a composition close to $MO_{2\cdot32}$. The one case where some unoxidised material was still present when the average composition was slightly richer in oxygen than $MO_{2\cdot32}$ could be explained by some formation of " phase B," the lines being too faint to appear. Finally, oxidation at 600° caused the complete disappearance of the fluorite structure; the product was almost certainly one phase and its structure was probably orthorhombic because of the strong similarity of the *X*-ray diffraction pattern to that of U_3O_8, though the positions of the diffraction lines showed that the cell size differed from that of U_3O_8. A complete structure determination has not been carried out, but low-angle lines on the *X*-ray pattern could be satisfactorily indexed by analogy with the U_3O_8 lines, and preliminary values of the cell constants are $a = 6\cdot75$, $b = 3\cdot97$, $c = 4\cdot15$ k.X.U. Zachariasen's values for U_3O_8 are $a = 6\cdot70$, $b = 3\cdot98$, $c = 4\cdot14$ k.X.U. (National Nuclear Energy Series VIII—5, 271). The oxidation of $U_{0\cdot82}Th_{0\cdot18}O_2$ below 200° yielded fluorite phases and stopped at the composition $MO_{2\cdot32}$. The fluorite phases were stable towards high temperatures *in vacuo*, but oxidation at high temperatures again gave a U_3O_8-like phase, presumably orthorhombic; preliminary values of the cell constants are $a = 6\cdot81$, $b = 3\cdot94$, $c = 4\cdot17$ k.X.U.

The oxidation in air or low-pressure oxygen of mixed crystals containing less than 80 moles % of uranium dioxide always yielded cubic phases, but oxidation of $U_{0\cdot66}Th_{0\cdot34}O_2$ in 120 atm. of oxygen at 550° broke the fluorite structure to give a phase of lower symmetry, shown by the splitting of the low-angle lines of the diffraction pattern; the structure could not be determined since the lines were very diffuse.

The products of the oxidation in air at 200—400° of mixed crystals containing less than 80 moles % of uranium dioxide were sometimes single fluorite phases and sometimes mixtures of two fluorite phases, one of which was the unoxidised material. Oxidation to completion—a limit when no more oxygen could be absorbed by the solid—at low or high

TABLE 2.

	Oxidation treatment:		Composition limit of fluorite phase:			Oxidation treatment:		Composition limit of fluorite phase	
x in $U_xTh_{1-x}O_2$	Max. temp.	Conditions	U valency	y in MO_{2+y}	x in $U_xTh_{1-x}O_2$	Max. temp.	Conditions	U valency	y in MO_{2+y}
1·0	180°	5—15 cm. O_2	4·58	0·29	0·24	360	5—15 cm. O_2	5·31	0·16
0·90	120	,,	4·70	0·315		450	120 atm. O_2	5·38	0·17
0·82	185	,,	4·79	0·32				5·45	0·18
0·78	400	,,	4·85	0·33		400	1 atm. NO_2	5·40	0·18
0·76	570	,,	4·88	0·34	0·146	370	5—15 cm. O_2	5·36	0·096
0·66	500	,,	5·07	0·34		450	120 atm. O_2	5·46	0·11
0·50	320	Air	5·21	0·30	0·063	400	5—15 cm. O_2	5·08	0·034
	500	120 atm. O_2	5·26	0·32		450	100 atm. O_2	5·37	0·043
0·38	500	Air	5·16	0·22	0·030	500	5—15 cm. O_2	4·94	0·014
	650	120 atm. O_2	5·26	0·24	0·010	420	,,	4·51	0·0026
	400	1 atm. NO_2	5·39	0·27					

temperatures always gave a single-phase product, and the intermediate two-phase materials gave a single-phase product after annealing in evacuated sealed tubes at ~800°.

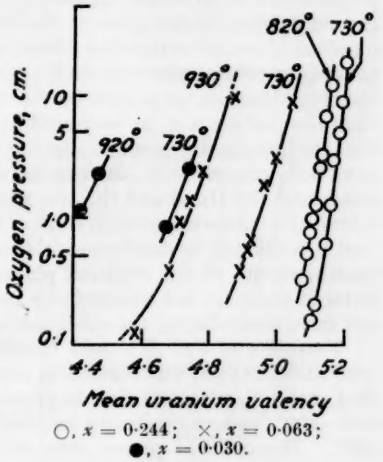
The Compositions of the Cubic Oxidised Phases.—The highest oxygen concentrations found in the fluorite phases, and the conditions of oxidation employed, are summarised in Table 2. The determination of these limits in the cases of the crystals containing 90 and 82 moles % of uranium dioxide has been discussed above. The limit of $UO_{2\cdot29}$ is quoted

for uranium dioxide itself since this is the highest oxygen content observed without definite evidence of the formation of a tetragonal oxide. In the other cases, the limit was determined by oxidising in air or in 5—15 cm. of oxygen for a long time at low temperatures and slowly raising the temperature in stages, allowing time for the oxidation to have apparently ceased at each temperature. At high temperatures the oxygen content began to decrease. The values in Table 2 are the highest observed, which were usually reached at ~400°. The oxygen content of fluorite phases formed by oxidation with high-pressure oxygen and with nitrogen dioxide are also included.

The mixed crystals having a uranium dioxide content of greater than 50% all oxidised to a gross composition of $MO_{2\cdot32}$—$MO_{2\cdot34}$ while retaining the fluorite structure, irrespective of the average uranium valency reached. The composition limit is thus dependent essentially on the geometry of the structure—on the additional oxygen that can be accommodated in the volume of the whole crystal; the density results presented below prove that the additional oxygen in the fluorite phases always enters interstitial positions. The composition limit tends to rise slightly as the uranium dioxide content decreases from 100 to 66 moles %, in accordance with the continuous expansion of the unit cell as Th^{4+} replaces U^{4+}.

Geometrical considerations cannot limit the amount of oxygen entering the crystals which are dilute in uranium. The maximum theoretical valency of uranium is 6. The maximum valency reached by the uranium in these experiments was 5·46, reached by oxidising $U_{0\cdot15}Th_{0\cdot85}O_2$ with high-pressure oxygen. The crystals more dilute in uranium actually took up less oxygen per uranium atom than the crystals with 15 and 25 moles % of uranium dioxide under the same oxidation treatment. These compositions are determined by thermodynamic considerations and not by purely structural factors.

FIG. 1. *Oxygen pressures in equilibrium with oxidised solid solutions, $U_xTh_{1-x}O_{2+y}$, plotted against the mean valency of the uranium.*



○, $x = 0\cdot244$; ×, $x = 0\cdot063$; ●, $x = 0\cdot030$.

The oxygen content of the mixed crystals in the dilute uranium range was a function of the temperature and the pressure of oxygen. Results for several mixed crystals are plotted in Fig. 1, the equilibrium pressures being plotted on a logarithmic scale for convenience; these equilibria could be approached from either direction, the time taken to come to equilibrium varying from about 15 min. at 600° to 2 min. at 900°. It was not possible to make equilibrium measurements at pressures greater than 30 cm., but the compositions reached on oxidation for at least 24 hr. at 120 atm. and at 500—600° were in reasonable agreement with extrapolated curves. These results and those in Table 2 illustrate that the compositions of the solid phases are determined by the magnitude of the free-energy changes on transfer of oxygen from the gas phase into the solid and that these are dependent on the particular configuration of uranium ions in the solid; the oxidised phases cannot be regarded as solid solutions of thorium dioxide and any known higher oxide of uranium.

Densities of the Fluorite Phases.—The densities of several of the mixed crystals which oxidised to give fluorite phases only were measured before and after oxidation in air at 500°. The results are recorded in Table 3. The calculated densities were obtained from the measurements of the unit-cell edge, by assuming no vacancies and 4 MO_2 " molecules " per unit cell. The density always increased on oxidation, and the amount by which it increased was in reasonable quantitative agreement with a theoretical increase calculated by assuming that the oxygen entered interstitial positions in the MO_2 lattice, allowance being made for the cell contractions observed (Table 1 and below). These results prove that the oxygen enters interstitial positions in the fluorite lattice at all uranium con-

centrations from 15 to 78 moles %, since any formation of cation defects would have been shown by a large fall of density on oxidation.

It is noteworthy that the measured densities of the reduced phases are always 2% and in one case nearly 6% lower than the calculated value. Such discrepancies are not due to poor penetration of pores in particles by the measuring fluid, since they occur even when helium is used; we have found similar results when measuring the densities of several

TABLE 3. *Densities of the fluorite phases,* $U_xTh_{1-x}O_{2+y}$.

Reduced phase			Oxidised phase			
	d (g./c.c.):			*d* (g./c.c.)	Density increase:	
x	obs.	calc.	*y*	obs.	obs.	calc.
0·146	10·00	10·15	0·10	10·03	0·03	0·07
0·244	9·94	10·25	0·16	10·00	0·06	0·12
,,	,,	,,	0·16	10·13	0·19	0·12
,,	9·68	10·25	0·16	9·82	0·14	0·12
0·498	10·27	10·47	0·30	10·50	0·23	0·28
0·783	10·52	10·72	0·33	10·81	0·29	0·42

preparations of uranium dioxide itself by using helium. Densities 6—10% lower than theoretical may be due either to the occurrence of a large number of Schottky defects, equal numbers of vacant cation and vacant anion sites, in the reduced crystals, or to an imperfect packing of crystallites in the solid particles. We found that low densities occurred when the crystallite size, as gauged by the width of the *X*-ray diffraction lines, was much smaller than the particle size, as measured by gas-adsorption methods, and it is therefore probable that the low-density preparations had a faulty microstructure, though Schottky defects may have been present also. Microstructure faults may explain the low density of one preparation made by Hund and Niessen, which led them to postulate that cation defects and not interstitial anions occurred in some of the oxidised phases. The results in Table 3 illustrate that it is difficult to decide unequivocally the type of defect present on the basis of density measurements of the oxidised phases if the densities of the same preparations in the reduced state are not available for comparison. Our results show that cation defects are not introduced during the oxidation of these mixed crystals.

Variation of Cell Size with Composition.—The variation of cell size with amount of interstitial oxygen was studied in detail on crushed-crystal samples of the 14·6, 24·4, and 38·4 moles % uranium dioxide preparations. Most of the preparations were annealed at 600—800°; where this might have caused loss of oxygen, they were held for some hours at 400°. The oxidised phases were all single-phase and well crystallised. The results are plotted, as a_{100} against the average uranium valency reached, in Figs. 2*a*, *b*, and *c*. The behaviour is very similar in the three cases when they are compared on a basis of uranium valency reached. A regular and probably linear contraction of the unit cell occurs at first, a shallow minimum is reached around a uranium valency of 5·0, and the cell expands as the uranium valency increases to 5·5. In order to make a quantitative comparison, the quantity $\Delta a/x$ for all three crystals is plotted against average uranium valency in Fig. 3; here Δa is the difference in a between the oxidised and reduced crystal and x is the mole % of uranium dioxide in the reduced crystal. This is equivalent to plotting the cell contraction per unit concentration of interstitial oxygen against uranium valency. The points for the three crystals all lie near to one curve, and the $\Delta a/x$ values for a given valency are in reasonable agreement with similar values calculated for crystals of higher uranium content whose oxidation cannot be carried so far. Thus, at a uranium valency of 4·7, the crystals containing 90 and 82 mole % of uranium dioxide give $\Delta a/x$ values of 0·033 and 0·032, respectively, while the curve in Fig. 3 passes through $\Delta a/x = 0{\cdot}031$. Further, the limiting straight line followed from a uranium valency of 4·0 to 4·4 has a slope of −0·044 per unit valency increase, or −0·09 k.X.U. per oxygen atom added, a value only slightly less than the value of −0·12 Å per oxygen atom found in the uranium dioxide–oxygen system by Perio (*Bull. Soc. chim.*, 1953, 256). It therefore seems that the cell contraction caused by a given quantity of interstitial oxygen per uranium atom is independent of the concentration of uranium in the crystal, at least as a first approximation.

The change from cell contraction to cell expansion as the uranium valency passes

through 5·0 is accompanied by a marked change in colour. The crystals containing 25 and 15 moles % of uranium dioxide change from a pure green (U^{4+} colour) to grey-black as the uranium valency increases from 4 to 5; when this valency is 5·2, the colour is brown-black and at a valency of 5·4 the colour is a rich brown. The corresponding colour sequence of the crystal having 6 moles % of uranium dioxide is light green—straw—dirty straw—red-brown.

FIG. 2*a*. *Variation of cell constant with oxidation state, for the solid solution* $U_{0\cdot38}Th_{0\cdot62}O_2$.

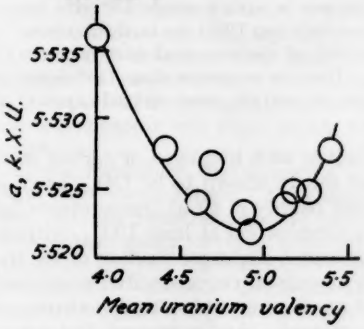


FIG. 2*b*. *Variation of cell constant with oxidation state, for the solid solution* $U_{0\cdot24}Th_{0\cdot76}O_2$.

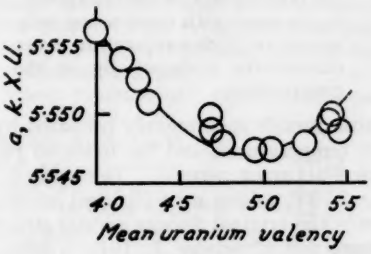
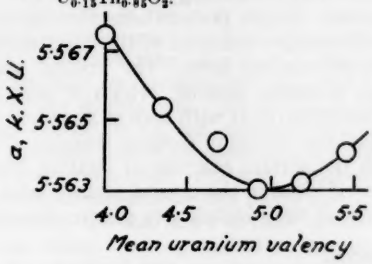
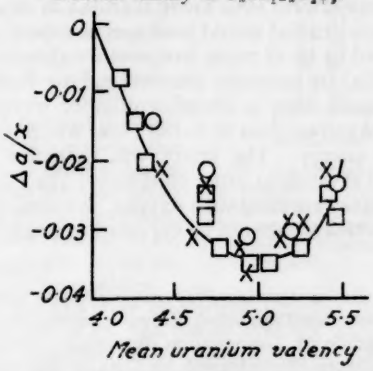


FIG. 2*c*. *Variation of cell constant with oxidation state, for the solid solution* $U_{0\cdot15}Th_{0\cdot85}O_2$.



○, $x = 0\cdot146$; □, $x = 0\cdot244$; ×, $x = 0\cdot384$.

FIG. 3. *Plot of* $\Delta a/x$ *against the average uranium valency in* $U_xTh_{1-x}O_{2+x}$.



The minimum in the plot of Fig. 3 and the colour changes indicate that the type of interaction between uranium and oxygen alters as the uranium valency is increased beyond 5·0. That the cell contracts as interstitial oxygen is first added may be due to the contraction following upon an effective increase of charge outweighing the expansion due to the inclusion of additional oxygen. This might be expected if U^{5+} were formed instead of U^{4+}. The expansion of the cell as some of the uranium has to become sexavalent, whatever the concentration of interstitial oxygen in the crystal as a whole, would then mean that sexavalent uranium can only occur through the formation of groups such as $(UO)^{4+}$ or $(UO_2)^{++}$, with consequent lowering of the coulombic energy of the crystal. The formation of linear groups such as $(UO_2)^{++}$ is possible along the diagonals of the (110) planes.

This work was started during the tenure by one of us (E. W.) of a Vacation Studentship at A.E.R.E., Harwell. We are indebted to Dr. R. W. M. D'Eye for help with some of the *X*-ray work and to Mr. E. A. Harper for some of the density measurements.

ATOMIC ENERGY RESEARCH ESTABLISHMENT,
HARWELL, DIDCOT, BERKS.

[*Received, April 13th*, 1954.]

The Oxides of Uranium. Part V. The Chemisorption of Oxygen on* UO_2 *and on* UO_2–ThO_2 *Solid Solutions.*

By L. E. J. Roberts.

[Reprint Order No. 5302.]

Oxygen is rapidly chemisorbed by freshly reduced surfaces of uranium dioxide at −183°, and also by surfaces of mixed crystals of uranium dioxide and thorium dioxide if these surfaces are prepared by crushing macrocrystalline samples. One oxygen molecule reacts with a single U^{4+} site in the primary act of chemisorption. At least half the U^{4+} ions in the surface layers react with oxygen and only about 30% of the occupied sites become vacant on high-temperature evacuation. There is evidence that Th^{4+} ions concentrate preferentially in the surface layers of some mixed-crystal preparations.

Uranium dioxide is commonly prepared by reduction with hydrogen or carbon monoxide at high temperatures, and the oxide so prepared can be shown to be $UO_{2\cdot0}$ as closely as analytical accuracy permits. The oxide is oxidised readily in air at temperatures between 100° and 180°, taking up additional oxygen to a composition at least $UO_{2\cdot25}$ without any change in the original fluorite crystal structure except a slight contraction of the unit cell (Anderson and Alberman, *J.*, 1949, S 303). The oxygen enters interstitial positions in the uranium dioxide lattice without the nucleation of a new phase at low temperatures, and the surface area remains unchanged as oxidation proceeds (Anderson and Roberts, to be published). It has been found that the solution of oxygen in uranium dioxide commences at temperatures even lower than the 27 kcal./mole activation energy of the bulk oxidation hitherto studied would lead one to expect; uranium dioxide preparations that have been exposed to air at room temperature always contain oxygen in excess of the stoicheiometric formula, in amounts proportional to their specific surface area. The present work is concerned with a chemisorption of oxygen on uranium dioxide, which is practically instantaneous even at −183°, and which must therefore occur with zero or very low activation energy. The study was extended to include uranium dioxide–thorium dioxide mixed crystals in order to discover the effect on the surface reaction of diluting the sites capable of reacting with oxygen, presumably the U^{4+} ions in the crystal surface, with Th^{4+} ions which would not be expected to react, because of their inability to donate electrons.

Experimental

Uranium Dioxide Preparations.—The preparation and properties of the uranium dioxide specimens used are listed below. Starting materials were "AnalaR" uranyl nitrate or the very pure grade of "ammonium diuranate" available in the atomic energy project. The preparations were characterised by: (i) *X*-Ray diffraction patterns, all of which showed the lines expected for the dioxide, with a cube cell edge of 5·457 ± 0·002 k.X.U. and a theoretical density of 10·96 g./c.c. The effective crystallite diameter, $\bar{a}$, was estimated from the half-width of the *X*-ray lines by comparison with a well-crystallised sample of particle size ~2·5 μ, the calculations being made by Jones's methods (*Proc. Roy. Soc.*, 1938, *A*, **166**, 16). (ii) The real density as measured with helium. (iii) The mean particle diameter, $\bar{d}$, calculated from the specific surface area as measured by B.E.T. analysis applied to the physical adsorption isotherms of nitrogen at −196° or of oxygen at −183° (Brunauer, Emmett, and Teller, *J. Amer. Chem. Soc.*, 1938, **60**, 309).

Key to designation of UO_2 *specimens.*

B1. Prepared by reducing the trioxide with hydrogen at 650°. Density 10·84 g./c.c., $\bar{d} = 0{\cdot}45$ μ, $\bar{a} = 0{\cdot}22$ μ.

C3. Prepared by reducing triuranium octoxide with carbon monoxide at 700°. Density 10·90 g./c.c., $\bar{d} = 0{\cdot}41$ μ, $\bar{a} = 0{\cdot}38$ μ. The particles were therefore probably single crystals.

H. A pure grade of commercial dioxide. Density 10·15 g./c.c., $\bar{d} = 1{\cdot}0$ μ, $\bar{a} = 0{\cdot}18$ μ. The low density and high d/a ratio suggested that the microstructure was complicated, each particle being probably composed of a large number of crystallites.

* Part IV, preceding paper.

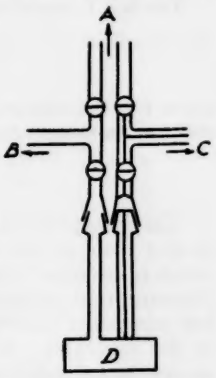
B50. Prepared by reducing the trioxide with carbon monoxide at 480°. $\bar{d} = 0{\cdot}053\ \mu$, $\bar{a} \sim 0{\cdot}05\ \mu$.

R. Prepared from specimen H by sintering at 2200° in a vacuum furnace, breaking the sintered pellet in a percussion mortar, and finely grinding the crystalline, glistening product in an agate mortar. The vacuum furnace was described by Alberman (*J. Sci. Instr.*, 1950, **27**, 280). The density was 10·85 g./c.c., $\bar{d} = 2{\cdot}3\ \mu$, $\bar{a} > 1\ \mu$. The particles were probably broken single crystals.

CA. Prepared from sample C3 by sintering at 2000° and crushing. $\bar{d} = 2{\cdot}3\ \mu$, $\bar{a} > 1\ \mu$.

Mixed-crystal Preparations.—Uranium dioxide and thorium dioxide form a continuous series of mixed crystals (Slowinski and Elliot, *Acta Cryst.*, 1952, **5**, 768). Two types of preparation were used. The first series of mixed crystals was prepared by coprecipitating the hydroxides from a mixed nitrate solution, drying, and reducing the product with carbon monoxide at 1200—1400°. Full details of these preparations are given in Part IV of this series (*loc. cit.*). The second series was made from the first by sintering at 1800—2100° and crushing the large crystals formed. All the precipitations were well-crystallised and had the expected apparent cell edge, which was a linear function of composition.

FIG. 1. *Adsorption bulb.*



A, to gas supply and pumps.
B, to McLeod gauge.
C, to mercury manometer and gas burette.
D, Adsorbent.

Adsorption Apparatus.—Measurements of gaseous adsorption could be made in two pressure ranges. A constant-volume mercury manometer was used for pressures above 10 mm., and read to ±0·2 mm.; a modified McLeod gauge measured pressures from 5×10^{-2} mm. to 6 mm. with an accuracy of ±2% above 0·1 mm. The powdered sample was contained in a "Vitreosil" U-tube, of which one limb was 1-mm. silica capillary and the other 5-mm. tubing. The capillary limb was connected by a cone-socket joint to the Pyrex capillary line joining the gas burette and constant-volume manometer, while the 5-mm. limb was connected through 5-mm. Pyrex tubing to the McLeod gauge. The arrangement is shown in Fig. 1. The high- and low-pressure measuring systems could be used independently on any one sample. During low-temperature adsorption measurements, the silica holder was surrounded by liquid oxygen or liquid nitrogen to a height of 2 in. above the sample bulb. At low pressures, the thermal gradient was thus carried by a 5-mm. diameter tube, and no thermomolecular flow corrections had to be applied to the pressure measurements so long as the pressure was >0·1 mm. The accuracy of the adsorption measurements varied according to the surface area of the adsorbent, being greater for the larger surface areas, but was judged to be generally better than ±3%. The temperature of the liquid-air baths was measured with an oxygen vapour-pressure thermometer.

B.O.C. "Spectroscopically Pure" oxygen and nitrogen were used without further purification. Hydrogen for reduction was obtained from a cylinder, and passed over hot platinised asbestos and through potassium hydroxide and magnesium perchlorate tubes. Carbon monoxide was obtained either by the action of sulphuric acid at 120° on formic acid or from a cylinder, and in each case was passed through potassium hydroxide, a liquid-oxygen trap, copper foil at 500°, potassium hydroxide, and a second liquid-oxygen trap. B.O.C. "Spectroscopically Pure" helium was used for determining the volumes of the gas leads and adsorption bulbs, and when used at low temperatures was first purified by passage through a charcoal trap at −195°. Taps were lubricated with Apiezon Grease "L" or "N" or with Dow Corning High Vacuum Silicone Lubricant if the taps were liable to get warm. Joints were made with Apiezon "W" wax.

Experimental Procedure.—The experiments essentially consisted of a comparison of adsorption isotherms of oxygen at −183° on "reduced" and "oxidised" surfaces of UO_2 and of the mixed crystals.

Reduction was carried out by streaming small volumes of hydrogen or carbon monoxide through the adsorption bulb at temperatures of 500—700°. The specimen was pumped out between each dose of reducing gas and the reduction continued until the amount of water or carbon dioxide that could be frozen out of the issuing gas had fallen to a constant low value. The specimen was then normally pumped out at 50° above the temperature of reduction until the system held a pressure <1 μ when isolated from the pumps, which generally took about 30 min. The specimen was then cooled in liquid oxygen for 1—2 hr., or for at least 30 min. if about 1 cm. of purified helium was added to aid the attainment of thermal equilibrium. The

helium was pumped off, oxygen admitted, and adsorption measurements commenced. Equilibrium was apparently established in a few minutes if the gas pressure was higher than 1 cm.; equilibrium times were of the order of 30 min. if the pressure was lower than 1 mm.

After this determination of the oxygen adsorption isotherm on a " reduced " surface, the sample was either (*a*) pumped at −183° for ½—1 hr. and at −80° for 10 min., or (*b*) allowed to oxidise at 0° or 23° until the rate of oxidation became low, and then outgassed for 5 min. at 0° or 23°. The sample was then cooled to −183° as before, and a second adsorption isotherm of oxygen at −183° determined; this was the isotherm characteristic of an " oxidised " surface. Any variations of this procedure are discussed with the results. All the gas adsorbed during the determination of the second isotherm could be recovered by warming the adsorbent to 25°. Adsorption on the oxidised surface was therefore taken to be physical adsorption only. If the isotherm on the oxidised surface had not been determined in a pressure range suitable for treatment by the B.E.T. equation, the isotherm was redetermined at relative pressures (p/p_0) of ~0·02 to 0·15. In some cases, the physical adsorption of nitrogen was measured in the same pressure range at −196°.

The B.E.T. equation was used in the simple form:

$$\frac{p/p_0}{V(1 - p/p_0)} = \frac{p/p_0}{V_m C} + \frac{C - 1}{V_m C}$$

where V is the volume of gas adsorbed at a relative pressure p/p_0, V_m is the monolayer volume, and C a constant related to the heat of adsorption.

Results and Discussion

The adsorption of oxygen on the reduced surfaces at −183° and at any pressure was greater than on the oxidised surfaces, except in the case of some of the mixed crystals, which is discussed below. Two typical isotherms are shown in Fig. 2. It was clear that chemisorption occurred on the reduced surfaces at −183°; it was complete within a few minutes of admitting oxygen, and this time was probably due only to the dimensions of the apparatus; the amount chemisorbed at −183° showed no signs of increasing in several hours' exposure. At higher temperatures an additional, time-dependent reaction occurred. A plot of the total amount of oxygen reacting at 0° against time of exposure for three samples of the C3 specimen is shown in Fig. 3: oxygen was admitted to the reduced surface at 0° in two cases, and in the third case was admitted first at −183° and subsequently at 0°. The amounts reacting are divided by $V_m(N_2)$, the amount of nitrogen required to form a physically adsorbed monolayer calculated from the B.E.T. equation in order to correct for small differences in surface area introduced during the high-temperature reduction process. The results showed that the total attack at 0° was the sum of two processes, one of which was complete at −183°.

The amounts chemisorbed were calculated by direct subtraction of the isotherm relating to the oxidised surface from that determined on the reduced surface, as in Fig. 2. If the oxygen had been pumped off at −183° and −80° after the first isotherm and the second determined immediately, the two curves were accurately parallel over the whole pressure range ($p/p_0 = 10^{-4}$ to 10^{-1}). If oxidation at higher temperatures had occurred before the determination of the physical adsorption isotherm, the two isotherms were parallel at higher pressures ($p/p_0 = 10^{-2}$ to 10^{-1}), as in Fig. 2, but some divergence occurred at relative pressures below 10^{-3}, the apparent amount chemisorbed being larger at lower pressures. This effect seemed to be due to a change in the heat of physical adsorption of oxygen on the oxidised surface caused by the high-temperature oxidation. Such a change would particularly affect the physical adsorption isotherm at low relative pressures; around $p/p_0 \sim 0{\cdot}1$, where a physically adsorbed monolayer would be nearly complete, small changes in heats of adsorption would affect the isotherm less.

Hence, if oxidation had occurred at 0° or above, the physical adsorption was determined only at the higher relative pressures; when it was necessary to determine the amount chemisorbed at low pressures, because the amount was small, the temperature of the specimen was not raised above −80° between the two isotherms. Direct comparisons of the amounts chemisorbed by determining the physical adsorption isotherm at high

pressures (*a*) after pumping at −80° and (*b*) after bulk oxidation gave results in agreement within 5%.

Chemisorption on Uranium Dioxide.—The volume of oxygen (V_0 c.c., N.T.P.) chemisorbed at −183° on various samples of uranium dioxide is recorded in Table 1, together with the essential details of the treatment of the sample before the isotherms were determined, and the values of $V_m(O_2)$, the volume of oxygen at N.T.P. required to form a monolayer of physically adsorbed oxygen on the surface of the sample, as calculated by the B.E.T. equation from the oxygen isotherm on the oxidised surface. Since $V_m(O_2)$ was determined after oxidation at very low temperatures, the value was characteristic of the surface upon which chemisorption had occurred. Changes in the extent of the adsorbing surface of a particular sample occurred only during the high-temperature reduction processes, and were probably connected with the tendency of the oxidised uranium dioxide samples to split into two phases of constant composition ($UO_{2\cdot0}$ and U_4O_9) at temperatures a little below those at which rapid reduction occurred (>450°). Increases in surface area

FIG. 2. *Adsorption of oxygen at −183° on reduced and oxidised surfaces of uranium dioxide.*

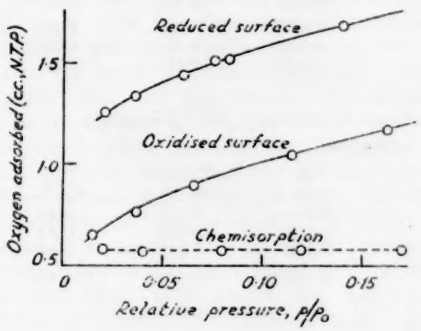
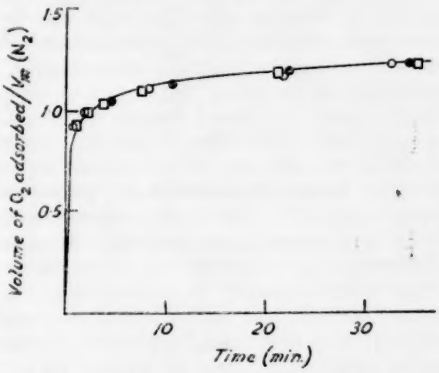


FIG. 3. *Oxygen absorption by uranium dioxide at 0°.*



□ Oxidation at 0° and 17 cm. pressure after chemisorption at −183°; $V_m(N_2)$ = 0·373 c.c./g.
○ Oxidation at 0° and 12 cm. pressure; $V_m(N_2)$ = 0·404 c.c./g.
● Oxidation at 0° and 12 cm. pressure; $V_m(N_2)$ = 0·410 c.c./g.

due to particle division on high-temperature annealing have been observed. The final surface after any reduction was then the result of two competing processes: particle division and the sintering of some of the smaller particles, which was shown in separate experiments to occur at all temperatures above 500°. Hence the surface on which chemisorption took place was at least partly a fresh surface in each experiment, even on the same specimen of UO_2.

The amount of oxygen chemisorbed was remarkably independent of all factors except the extent of the adsorbing surface. The last column in Table 1 gives the values of the ratio $V_0/V_m(O_2)$, the amount of oxygen chemisorbed per standard area of surface. All V_0/V_m values were between 0·3 and 0·9, independent of the temperature at which the uranium dioxide had originally been produced or at which reduction took place before chemisorption, of which reducing gas was used, and of whether the preparation consisted of broken crystals (CA and R) or of dioxide as prepared by reduction of a higher oxide. Some systematic variations in $V_0/V_m(O_2)$ values occurred. The average value of V_0/V_m for those preparations which had never been in hydrogen (C3, CA, and B50) was 0·64 and for the two in closest agreement (C3 and CA) 0·55, while the average V_0/V_m value for those reduced with hydrogen (B1, H, and R) was 0·45. This difference can be ascribed to a change in surface properties following upon the chemisorption of hydrogen.

It has been found that uranium dioxide is capable of chemisorbing hydrogen in quantites at least sufficient to form a complete monolayer by an activated process that occurs rapidly above 550°. It is difficult to remove the hydrogen quantitatively even at considerably higher temperatures, and the pumping conditions employed here after reduction by hydrogen may well have been insufficient to remove all chemisorbed gas. A direct test

TABLE 1.

UO_2 sample	Treatment of sample: before 1st isotherm	before 2nd isotherm	V_0, c.c./g.	$V_m(O_2)$, c.c./g.	V_0/V_m
C3	CO, 580°	O_2, 0°	0·220	0·403	0·55
	CO, 700	Pumped −80	0·183	0·321	0·57
	CO, 580	Pumped −80	0·210	0·403	0·52
CA	CO, 700	O_2, 0	0·0295	0·052	0·57
	CO, 700	O_2, 0	0·0300	0·057	0·54
B50	CO, 480	Pumped −80	2·30	2·71	0·85
	CO, 480	O_2, 20	2·40	2·69	0·86
B1	H_2, 550	O_2, 22	0·185	0·332	0·56
	H_2, 740	O_2, 22	0·168	0·332	0·51
	H_2, 530	O_2, 22	0·146	0·320	0·46
	H_2, 500	O_2, 22	0·171	0·311	0·55
H	H_2, 500	O_2, 0	0·065	0·139	0·47
	H_2, 550	O_2, 22	0·059	0·133	0·45
R	H_2, 500	O_2, 23	0·0262	0·069	0·38
	H_2, 500	O_2, 22	0·0238	0·062	0·39
	H_2, 700	O_2, 22	0·0148	0·051	0·29

TABLE 2. *Adsorption of oxygen on uranium dioxide at −183° following chemisorption of hydrogen.*

Sample	Hydrogen chemisorbed, c.c./g.	Temp. at which H_2 removed	V_0, c.c./g.	$V_m(O_2)$, c.c./g.	V_0/V_m
B1	0·23	22°	0·151	0·332	0·46
	0·42	22	0·146	0·332	0·44
	—	740	0·185	0·332	0·56
C3	0·34	200	0·165	0·354	0·47

TABLE 3.

Sample	Reduction conditions	V_0, c.c./g.	Pumping conditions after O_2 chemisorption: Time	Temp.	V_1, c.c./g.	V_1/V_0
B1	H_2, 550°	0·185	30 min.	22°	0·034	0·18
			30 ,,	140	0·050	0·27
			30 ,,	400	0·060	0·33
R	H_2, 700	0·0148	3 hr.	25	0·0051	0·33
			24 ,,	25	0·0033	0·21
			1 ,,	150	0·0033	0·21
C3	CO, 580	0·220	16 ,,	25	0·0078	0·035
			2 ,,	170	0·043	0·20
$U_{0·82}Th_{0·18}O_2$	CO, 750	0·290	16 ,,	25	0·060	0·21

showed that the chemisorption of hydrogen lowered the V_0/V_m value for subsequent oxygen chemisorption. The results of two experiments in which $V_0/V_m(O_2)$ values were determined in the usual way on surfaces of uranium dioxide that had chemisorbed known quantities of hydrogen and then been outgassed at temperatures sufficiently low, so that none of the hydrogen was removed, are given in Table 2. It is apparent that the $V_0/V_m(O_2)$ value characteristic of a hydrogen-covered surface is 0·46—0·48, and that prolonged pumping at 740° causes the $V_0/V_m(O_2)$ value to rise to 0·57, in agreement with values found after reduction by carbon monoxide (Table 1). This gas is not chemisorbed at high temperatures to anything like the extent that hydrogen is. A small chemisorption was observed, reaching, at constant pressure, a maximum of ~8% coverage at ~250°, and falling to barely measurable amounts above 600°. No carbon dioxide was formed when the monoxide was

left in contact with a fully reduced C3 sample for 10 hr. at temperatures between 670° and room temperature.

It seems fair to conclude that the $V_0/V_m(O_2)$ values on specimens reduced by carbon monoxide were characteristic of " clean " uranium dioxide surfaces. It is not clear why the $V_0/V_m(O_2)$ ratio rose to 0·9 on the B50 sample, but this is probably due to the highly disordered, " active " nature of the surface of this specimen, which had been made at relatively low temperatures (480°), consisted of very small particles, of about 500 Å diameter, and was poorly crystalline. The other anomaly is the values below 0·4 which were determined on one of the crushed crystal samples (R), though the other crushed crystal sample (CA) showed normal behaviour. It is possible that sample R had been " poisoned " more extensively by hydrogen, or that the crystals had cleaved in a different way when crushed, to expose less active surfaces.

The chemisorbed layer formed at −183° remained complete so long as the dioxide was in contact with oxygen, *i.e.*, the second or physical adsorption isotherm on any one sample remained essentially unchanged whether oxidation occurred at 0°, 25°, or 135°. (These results are not recorded in Table 1 since only the low-pressure parts of the isotherms were determined.) The results in Table 1 show that no additional chemisorption took place on readmitting oxygen to a uranium dioxide surface that had been exposed to oxygen at −183° and then pumped at −80°. But some additional chemisorption did occur when the chemisorbed layer was pumped at higher temperatures. The results are collected in Table 3. The V_0 values were determinated as before from −183° isotherms on the freshly reduced and fully oxidised surfaces, and the V_1 values quoted are the additional chemisorption found after the oxygen had been removed from the original chemisorbed layer at −183° and −80° and the uranium dioxide sample pumped at the temperature shown in Col. 3 of Table 3; V_1 was calculated by subtracting the −183° isotherm on the fully oxidised surface from that obtained after the given pumping treatment. The experiments are quoted in chronological order, and it is clear that a certain amount of oxygen can be lost from surface sites at 25° whatever the previous history of the specimen, so long as bulk oxidation has been avoided. The results on the three samples of uranium dioxide are in reasonable quantitative agreement for the experiments in which the evacuation was carried out at 140—170°, when about 25% of the original chemisorbed layer was lost from the surface sites. Only about 33% was lost even on heating to 400°. One result on an 82 mole-% uranium dioxide–thorium dioxide mixed crystal is included in Table 4; the behaviour was very similar to that of uranium dioxide itself.

The surface oxygen is far less mobile than the previous bulk oxidation studies might suggest. Anderson and Alberman (*loc. cit.*) found that the bulk oxidation proceeded with an activation energy of 27·5 kcal./mole between 100° and 180°, which they ascribed to the energy required to move an oxygen atom from one interstitial position to the next in the uranium dioxide lattice. From their measured diffusion coefficients it can be calculated that each uranium atom should travel a mean distance inwards of 40 Å in 30 min. at 175°, and this conclusion is borne out by the fact that uranium dioxide which has reacted with oxygen at 0° for 30 min. and then been pumped for a short time at 150° absorbs more oxygen at nearly the same rate as it initially did when next exposed to oxygen at 0°.

Hence at least 70% of the chemisorbed oxygen is far more firmly bound to the surface sites than is oxygen than has already entered the uranium dioxide lattice. This conclusion is supported by some preliminary measurements of the heat of adsorption of oxygen at −183°, which may be as high as 50 kcal./mole on a clean dioxide surface, and which falls as the surface layer becomes completed.*

Chemisorption on Uranium Dioxide–Thorium Dioxide Mixed Crystals.—The chemisorption of oxygen at −183° was measured on a series of mixed crystals in the same manner as on uranium dioxide; all the reductions were carried out with carbon monoxide. The results are shown in Fig. 4, $V_0/V_m(O_2)$ values being plotted against the composition of the crystals, expressed as moles % of uranium dioxide. There was a profound difference

* The author is indebted to Mr. J. D. M. McConnell for this information and for permission to mention it before publication.

between the behaviour of mixed crystals as reduced at 1200—1400° and of crushed crystals. Chemisorption per unit surface on the crushed crystals was a roughly linear function of the uranium content at least down to 15 moles % of uranium dioxide, while chemisorption on the samples as reduced fell to very low values below 57 moles % of uranium dioxide.

This difference was further illustrated by comparing the amount of oxidation occurring at 0° or 23° for the various specimens. The quantities of oxygen absorbed in the first 30 min. are collected in Table 4; after 30 min., the rate of oxidation became slow (Fig. 2). Longer times are recorded in Table 4 for the slower reactions. Pressures of oxygen were between 3 and 11 cm. The quantities recorded (V) do not include the oxygen chemisorbed at −183°. The $V/V_m(O_2)$ ratios are recorded in order to make a valid comparison of reaction rates. The rate was at least a factor of 10 higher on the crushed crystals having low uranium concentrations than on the reduced samples.

These results imply that Th^{4+} ions had been preferentially concentrated in the surface layer or layers of the reduced mixed crystals in the dilute uranium range. Surfaces that had been generated by crushing large crystals almost certainly contained a representative

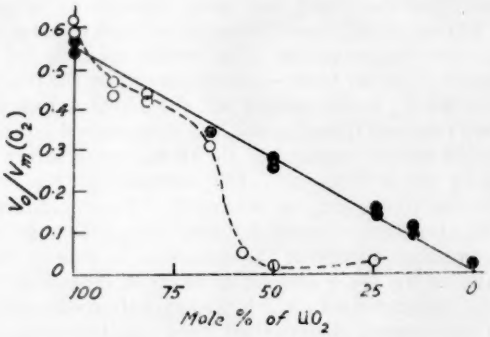


FIG. 4. *The chemisorption of oxygen at −183° on mixed crystals of uranium dioxide and thorium dioxide.*

● Crushed crystal preparations.
○ As reduced preparations.

fraction of the U^{4+} and Th^{4+} cations, which must, from the crystallographic evidence, be randomly distributed throughout the bulk of the crystals. The preferential concentration of Th^{4+} ions in the surface of the reduced specimens could be a consequence of the equilibrium surface at 1300° not containing a random selection of cations, or it may have occurred during the coprecipitation process that was the first stage in the manufacture of these solid solutions.

The linear dependence of $V_0/V_m(O_2)$ on the mole-fraction of uranium dioxide, for surfaces that almost certainly contained a random distribution of U^{4+} and Th^{4+} cations, suggests that the primary act of chemisorption of oxygen at −183° involves the interaction of an oxygen molecule with a single U^{4+} site. In a face-centred array of cations, each cation has 4 nearest cation neighbours and thus most U^{4+} cations in a 25 moles % solution and almost all in a 15 moles % solution would be surrounded by Th^{4+} cations; it is unlikely that direct co-operation between two U^{4+} sites could occur. It is not clear from these considerations alone how many electrons are effectively transferred to the oxygen, or whether the molecule of oxygen dissociates in the primary act of chemisorption or not.

Extent of Surface Coverage.—The extent of the adsorbing surface may be calculated from $V_m(O_2)$ or $V_m(N_2)$ if an area is assumed for a physically adsorbed molecule. The area of 16·2 Å^2 for the nitrogen molecule at −196° is usually taken as a standard. The area of the oxygen molecule at −183° may be calculated from the density of the liquid to be 14·1 Å^2, and the ratio $V_m(N_2)/V_m(O_2)$ should therefore 1/1·15. The mean of four determinations of this ratio on various UO_2 samples was 1/0·97, and, to facilitate comparison with other work, the effective area of the oxygen molecule will be assumed to be 16·7 Å^2. Measurements of surface area are in any case not generally considered accurate in the absolute sense to better than ±25%.

The calculation of the number of U^{4+} sites in the surface is further dependent upon some assumption of the crystal planes that are outermost. The equilibrium surfaces and cleavage planes are likely to be planes of low index. The (100) planes, in the fluorite structure, consist alternately of O^{2-} and of U^{4+} ions; the (110) planes consist of both O^{2-} and U^{4+} ions and are electrically neutral. The area occupied by a U^{4+} ion is $a^2/2$ or 14·9 Å^2 in the (100) planes and $a^2/\sqrt{2}$ or 21 Å^2 in the (110) planes. The area per ion will increase for planes of higher indices. Thus the maximum number of U^{4+} ions per physically adsorbed oxygen molecule (16·7 Å^2) will be 1·12—0·80, *i.e.*, there cannot be more than

TABLE 4. *The oxidation of* $U_xTh_{1-x}O_2$ *preparations at* 0° *and* 23°.

Preparation Type	x	Oxidation conditions Temp.	Mean pressure, cm.	Time	O_2 absorbed, V, c.c./g.	$V_m(O_2)$, c.c./g.	$V/V_m(O_2)$
Crushed crystals	1·00	0°	7	30 min.	0·0332	0·0565	0·59
	0·66	0	9	,,	0·043	0·129	0·33
	0·50	0	7	,,	0·0134	0·051	0·26
	0·24	0	6	,,	0·0039	0·074	0·053
	,,	23	6	,,	0·010	0·070	0·143
	0·15	23	6	,,	0·00039	0·052	0·0075
As reduced	1·00	0	11	30 min.	0·27	(0·40)	0·67
	0·90	0	10	,,	0·59	1·04	0·57
	0·82	0	7	,,	0·33	0·65	0·53
	,,	23	8	,,	0·475	0·65	0·73
	0·66	0	6	,,	0·042	0·114	0·37
	0·57	23	3	,,	0·0004	0·021	<0·02
	0·50	23	4	48 hr.	<0·0005	0·035	<0·01
	0·24	23	5	16 ,,	<0·001	0·034	<0·03

about 1 surface U^{4+} ion per oxygen molecule physically adsorbed on UO_2. The value of 0·58 for the $V_0/V_m(O_2)$ ratio on UO_2 therefore implies that at least half the U^{4+} ions in the surface are active in chemisorbing oxygen at −183°, one oxygen molecule being assumed to react with one U^{4+} site. It is not possible to postulate particular sites for the chemisorption: virtually the whole surface is active. This type of chemisorption, taking place on the whole surface with zero or very low activation energy, differs from the chemisorption of oxygen on oxides such as cuprous oxide, which is an activated process, occurring slowly at room temperature, although at least a monolayer of oxygen may eventually be adsorbed (Garner, Stone, and Tiley, *Proc. Roy. Soc.*, 1952, *A*, **211**, 472). The case of uranium dioxide is more closely analogous to that of metals, which are covered by a chemisorbed layer of oxygen swiftly at −183° (Allen and Mitchell, *Discuss. Faraday Soc.*, 1950, **8**, 309; Brunauer and Emmett, *J. Amer. Chem. Soc.*, 1940, **62**, 1732); the similarity is possibly due to the ready availability of electrons in both cases.

The oxidation processes occurring at 0° and 25°, for which some results have been given, cannot be further surface processes; solution of oxygen in the uranium dioxide lattice must be involved, since the amounts of oxygen taken up in long times of exposure may be four times the amount chemisorbed at −183° and this is far too much to be accommodated on the surface on any reasonable model.

The author gratefully acknowledges help and criticism received from Dr. J. S. Anderson in the course of this work. He is indebted to Mr. D. N. Edgington for the mixed-crystal preparations and to Mr. E. A. Harper for the helium-density measurements.

ATOMIC ENERGY RESEARCH ESTABLISHMENT,
HARWELL, DIDCOT, BERKS.

[*Received, April 13th*, 1954.]

*The Oxidation of Phenylhydrazones. Part IV.**

By B. M. Lynch and K. H. Pausacker.

[Reprint Order No. 5320.]

(*a*) The acid-catalysed rearrangements of benzylazoxybenzene have been studied.

(*b*) "Bisazoxybenzyl" (Bamberger and Renauld, *Ber.*, 1897, **30**, 2278) has been shown to be ω-azoxytoluene.

(*c*) The phenylhydrazones of certain aromatic and heterocyclic aldehydes and ketones have been oxidised with perphthalic acid.

Oxidation of benzaldehyde phenylhydrazone with perbenzoic or perphthalic acid yields benzylazoxybenzene (Part I, *J.*, 1953, 2517; Witkop and Kissman, *J. Amer. Chem. Soc.*, 1953, **75**, 1975). The present paper reports further investigation of similar compounds.

Bergmann, Ulpts, and Witte (*Ber.*, 1923, **56**, 679) found that benzylazoxybenzene rearranges to *N*-benzoyl-*N'*-phenylhydrazine in acetic acid at 150° (for milder conditions, see Experimental section); this rearrangement is closely similar to both the isomerisation of primary nitro-compounds to hydroxamic acids in hot sulphuric acid (Lippincott and Mass, *Ind. Eng. Chem.*, 1939, **31**, 118) and the conversion of primary aliphatic azoxy-compounds into *N*-acyl-*N'*-alkylhydrazines in hot hydrochloric acid (Langley, Lythgoe, and Rayner, *J.*, 1952, 4191). Although Bergmann *et al.* (*loc. cit.*) state that benzylazoxybenzene is unaffected by boiling hydrochloric acid, we have found that it is converted into benzaldehyde (40%) and benzoylazobenzene (45%) on prolonged treatment with 10N-hydrochloric or sulphuric acid.

The formation of these products may be explained by assuming that part of the benzylazoxybenzene is first converted into *N*-benzoyl-*N'*-phenylhydrazine (Bergmann *et al.*, *loc. cit.*) and that this is oxidised by unchanged benzylazoxybenzene forming benzoylazobenzene and benzaldehyde phenylhydrazone; the phenylhydrazone would then hydrolyse forming benzaldehyde:

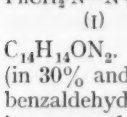
$$PhCH_2{\cdot}N(O){:}NPh \longrightarrow PhCO{\cdot}NH{\cdot}NHPh$$

$$PhCH_2{\cdot}N(O){:}NPh + PhCO{\cdot}NH{\cdot}NHPh \longrightarrow PhCO{\cdot}N{:}NPh + PhCH{:}N{\cdot}NHPh$$

$$PhCH{:}N{\cdot}NHPh + H_2O \longrightarrow PhCH{:}O + PhNH{\cdot}NH_2$$

This reaction sequence is analogous to the interaction of hydrazobenzene and azoxybenzene, with the formation of two molecules of azobenzene (Freundler, *Bull. Soc. chim.*, 1904, **31**, 459). Confirmatory evidence results from the formation of benzoylazobenzene in excellent yield when benzylazoxybenzene is refluxed with *N*-benzoyl-*N'*-phenylhydrazine in ethanolic hydrochloric acid.

In order to prepare benzylazoxybenzene by an alternative method, we attempted its synthesis from *N*-benzylhydroxylamine and nitrosobenzene. This reaction has already been studied by Bamberger and Renauld (*Ber.*, 1897, **30**, 2278), who obtained a product "bisazoxybenzyl," m. p. 210°, to which they assigned structure (I) ($C_{28}H_{28}O_2N_4$). Repetition of this work gave a product having the properties described by Bamberger and Renauld (*loc. cit.*), but our molecular-weight determinations indicate the molecular formula $C_{14}H_{14}ON_2$. It was shown to be identical (mixed m. p.) with ω-azoxytoluene, prepared (in 30% and 14% yield, respectively) by the peracid oxidation of both ω-azotoluene and benzaldehyde benzylhydrazone. As azoxybenzene was also isolated from the reaction, it appears that the products are formed by a mutual oxidation–reduction process:



(I)

$$2PhCH_2{\cdot}NH{\cdot}OH + 2PhN{:}O \longrightarrow PhCH_2{\cdot}N(O){:}N{\cdot}CH_2Ph + PhN(O){:}NPh$$

Such behaviour is common in these systems (cf. Taylor and Baker, "Sidgwick's Organic Chemistry of Nitrogen," Oxford, 1942, p. 432), although we used alkaline conditions, which

* Part III, *J.*, 1954, 1650.

favour the formation of unsymmetrical azoxy-compounds (cf. Bamberger and Bernays, *Ber.*, 1902, **35**, 1624; Aston and Jenkins, *Nature*, 1951, **167**, 863; Anderson, *J.*, 1952, 1722).

In addition to the azoxy-compounds described in Part I (*loc. cit.*), we have found that oxidation of the phenylhydrazones of several *ortho*-substituted benzaldehydes, and of thiophen-2-aldehyde phenylhydrazone, with perphthalic acid gives excellent yields of the corresponding azoxy-compounds. Furfuraldehyde phenylhydrazone gave a fair yield of azoxy-compound (cf. Bergmann *et al.*, *loc. cit.*) but *p*-dimethylaminobenzaldehyde phenylhydrazone gave a hygroscopic product which could not be purified satisfactorily. In this case, it is likely that *N*-oxide formation has also occurred at the tertiary nitrogen atom, as in the similar oxidation of *p*-dimethylaminophenylazobenzene (Angeli, *Atti R. Accad. Lincei*, 1915, **24**, 1190).

When benzaldehyde *N*-methylphenylhydrazone was oxidised with perphthalic acid, only a small yield of nitrosobenzene could be isolated. Oxidation of this hydrazone obviously cannot give an azoxy-compound. Only acetophenone was isolated from the peracid oxidation of acetophenone *N*-methylphenylhydrazone.

Experimental

(M. p.s are corrected. Microanalyses were performed under the direction of Dr. K. W. Zimmermann.)

Reactions of Benzylazoxybenzene in Acid.—(a) *Acetic acid.* Benzylazoxybenzene (3 g.) in glacial acetic acid (25 ml.) was refluxed (15 min.) and the solution poured into ice-water (100 ml.). The precipitate was crystallised from aqueous ethanol, giving needles (1·8 g.) of *N*-benzoyl-*N'*-phenylhydrazine, m. p. and mixed m. p. 168°.

(b) *Mineral acid.* Benzylazoxybenzene (2 g.) and 10N-hydrochloric or sulphuric acid (100 ml.) were refluxed (6 hr.). The mixture was distilled and the distillate added to a solution of 2 : 4-dinitrophenylhydrazine in hydrochloric acid. The precipitate was crystallised from glacial acetic acid, giving orange needles (0·90 g.), m. p. 234—236° (decomp.), undepressed on admixture with authentic benzaldehyde 2 : 4-dinitrophenylhydrazone.

The brilliant blue residue was dissolved in benzene–ethanol (1 : 1) and purified by chromatography on alumina, giving red plates (0·76 g.), m. p. 32—33°, identical with authentic benzoylazobenzene, which on reduction with zinc dust in acetic acid gave *N*-benzoyl-*N'*-phenylhydrazine, m. p. and mixed m. p. 168°.

(c) *Dehydrogenation of* N-*benzoyl*-N'-*phenylhydrazine.* Benzylazoxybenzene (1 g.) and *N*-benzoyl-*N'*-phenylhydrazine (1 g.) were refluxed (1 hr.) with 10N-hydrochloric acid (20 ml.) in ethanol (40 ml.). The solution was steam-distilled and the residue basified and extracted with ether. After evaporation and crystallisation of the residue from light petroleum (b. p. 30—90°), benzoylazobenzene (0·90 g.), m. p. 32°, was obtained.

Per-acid Oxidations.—(a) *Phenylhydrazones.* The phenylhydrazones listed below were oxidised by perphthalic acid in ethyl ether to the corresponding *azoxy*-compounds, as described in Part I (*loc. cit.*). The azoxy-compounds were crystallised from ethanol–pyridine.

Phenylhydrazone oxidised	Yield (%)	M. p. (decomp.)	Found (%) C	H	N	Required (%) C	H	N
o-Tolualdehyde	80	188°	74·2	6·0	12·5	74·3	6·2	12·4
o-Chlorobenzaldehyde	87	188	—	—	11·5	—	—	11·4
Salicylaldehyde	76	114·5	68·6	4·9	—	68·4	5·4	—
Furfuraldehyde	35	*ca.* 110—130	—	—	—	—	—	—
Thiophen-2-aldehyde	70	148·5	60·3	4·5 (S, 14·7)	—	60·5	4·6 (S, 14·7)	—

(b) N-*Methylphenylhydrazones.* Benzaldehyde *N*-methylphenylhydrazone (4 g.) and perphthalic acid (3·5 g.) in ethyl ether (50 ml.) were set aside for 4 days. Residual acids were removed in the usual manner, and the ether was evaporated. A portion (0·5 g.) of the residue (3·0 g.) was refluxed (30 min.) with aniline (0·5 ml.) in acetic acid (5 ml.). *trans*-Azobenzene (0·1 g.), m. p. and mixed m. p. 68°, was obtained after evaporation and crystallisation from ethanol.

Acetophenone *N*-methylphenylhydrazone (5 g.) was added to a solution of perphthalic acid (3·6 g.) in ethyl ether (100 ml.), and the solution shaken vigorously. After the solution had been set aside for 1 hr., phthalic acid was removed in the usual way. The ethereal solution was extracted with 2N-hydrochloric acid at 0°, and the acid layer was basified and extracted with

ether. Evaporation of this extract gave an oil which would not form a picrate. Evaporation of the original ether solutions and distillation of the residue gave acetophenone, b. p. 200° (phenylhydrazone, m. p. and mixed m. p. 105°).

(c) *ω-Azotoluene and benzaldehyde benzylhydrazone.* ω-Azotoluene [prepared by a method analogous to that used by Langley, Lythgoe, and Rayner (*loc. cit.*) for ω-azo-*p*-chlorotoluene] (2·8 g.) was added to a solution of perphthalic acid (5·5 g.) in ethyl ether (200 ml.), and the mixture was set aside in the refrigerator for 3 days. The precipitate was crystallised from *o*-xylene–ethanol, giving needles (1·0 g.) of *ω-azoxytoluene*, m. p. 209° (decomp.) (Found: C, 74·25; H, 6·2; N, 12·2. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2; N, 12·4%).

Similar oxidation of benzaldehyde benzylhydrazone gave the above azoxy-compound in 14% yield.

Attempted Synthesis of Benzylazoxybenzene.—*N*-Benzylhydroxylamine hydrochloride (Jones and Sneed, *J. Amer. Chem. Soc.*, 1917, **39**, 674) (4 g.), nitrosobenzene (4 g.), and sodium hydroxide (2 g.) in ethanol (200 ml.) were warmed to 40°, the solution becoming red-brown. The mixture was cooled and the precipitate crystallised from *o*-xylene, giving needles (2·5 g.), m. p. 209° (decomp.) undepressed on admixture with ω-azoxytoluene [Found: C, 74·4; H, 5·6%; *M* (Rast), 196. Calc. for $C_{14}H_{14}ON_2$: *M*, 226]. *trans*-Azoxybenzene, m. p. and mixed m. p. 36°, was isolated from the filtrate after evaporation and crystallisation from ethanol.

Thanks are expressed to Monsanto Chemicals (Australia) Limited for the award of a Research Scholarship to one of us (B. M. L.).

THE UNIVERSITY, MELBOURNE, N.3, VICTORIA, AUSTRALIA. [*Received, April 20th*, 1954.]

The Oxidation of Copper and Zinc.

By E. R. S. WINTER.

[Reprint Order No. 5336.]

It is found that the reaction $^{18}O_2 + {}^{16}O_2 \rightleftharpoons 2{}^{16}O{}^{18}O$ does not occur on the growing oxide film during the oxidation of copper at 50—110°, or zinc at 370—400°: initial oxygen pressures in both cases were *ca.* 3 cm. No exchange of oxygen with the films was observed. The observations are briefly discussed with reference to current theories regarding the mechanism of oxidation of these metals.

MUCH work has been devoted to the study of oxidation and tarnishing reactions on metals, and the results have been very valuable in developing the theory of the defect solid state. The general nature of the oxidation mechanism in terms of defect structures is believed to be understood in a number of cases, but little is known about details of the reaction.

The process being written very crudely as:

$$O_{2(g)} \rightleftharpoons O_{2(ads)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$O_{2(ads)} + 2M \longrightarrow 2MO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

and the nature of $O_{2(ads)}$ not being discussed for the moment, it is the second stage about which most is known. Some information about the first stage can be obtained by a detailed examination of the effect of oxygen pressure upon the overall rate of oxidation and upon the apparent activation energy. Such a study has been recently carried out on the oxidation of zinc by Moore and Lee (*Trans. Faraday Soc.*, 1951, **47**, 501). In order to explain their results they postulated, among other things, a reversible adsorption of oxygen as atoms on the zinc oxide surface; apart from this, their kinetic analysis contains an inconsistency which will be discussed elsewhere.

With a view to determine the nature of the adsorption step we have studied the oxidation of zinc foil (Johnson Matthey Spec. Pure) using Moore's technique of pre-oxidation with isotopically normal oxygen: the oxidation proper was followed by using a 1 : 1 mixture of normal oxygen and oxygen containing *ca.* 30% of ^{18}O so that the proportion of $^{18}O_2$ molecules in the gas was markedly greater than for a fully equilibrated gas containing

ca. 15% of ^{18}O. During the oxidation a representative small quantity of the oxygen in contact with the zinc oxide surface was bled off continuously into a mass-spectrometer and analysed at frequent intervals for masses 32, 34, and 36. This is essentially the technique we have used to study the oxygen exchange and equilibration reactions on solid oxide surfaces (*J.*, 1950, 1170, 1175; *J.*, 1954, 1509, 1517, 1522). At temperatures of 370° and 400° C and initial oxygen pressures of 2—5 cm. falling to zero, there was no equilibration of the oxygen; *i.e.*, the reaction

$$^{16}O_2 + {}^{18}O_2 \rightleftharpoons 2{}^{16}O{}^{18}O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

did not occur to a detectable extent although the rates of oxidation were appreciable. No isotopic exchange with the surface was detected. Using finely powdered zinc oxide containing interstitial zinc and prepared by burning pure zinc metal in air, we have shown (*J.*, 1954, 1522) that under similar conditions of temperature and pressure reaction (3) is catalysed by zinc oxide, with an apparent activation energy of 22 kcal. mole^{-1}, and proceeds more rapidly than the exchange of oxygen with the surface. The surface coverage with oxygen during these reactions is at most some 0·1%.

The conclusion seems clear that reversible adsorption/desorption of oxygen, *involving dissociation*, while possible on the powder, does not take place on the surface of zinc oxide in contact with the bulk metal. The temperatures involved are much less than $0{\cdot}5T_m$ (° K), where T_m is the melting point of zinc oxide (~2370° K), so that there should be no appreciable mobility of sub-surface ions (cf. Anderson *et al.*, *J.*, 1948, 1729; *Discuss. Faraday Soc.*, 1950, **8**, 238; Huttig, *Angew. Chem.*, 1936, **49**, 882); this we have confirmed in that the oxygen exchange reaction involves only the surface layer of oxygen ions (*J.*, 1954, 1517).

We suggest that the dissociative adsorption of oxygen is promoted by sub-surface interstitial zinc atoms, Zn_i, which at our temperatures are virtually immobile in the powdered zinc oxide: *e.g.*, by a reaction such as:

$$Zn_i + O_{2(g)} \rightleftharpoons 2O_{(ads)}^- + Zn_i^{2+} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

When the Zn_i atoms are immobilized in sub-surface layers this reaction will be reversible, and the $O_{(ads)}^-$, having some mobility over the surface (*J.*, 1954, 1522), will tend to desorb in partnership with ad-ions from other molecules, thus leading to equilibration. If the life on the surface is long enough there will also be a tendency for surface exchange to occur. [Incidentally, the presence on the surface of $O_{(ads)}^-$ of limited mobility may well cause the low-temperature semiconductivity, of small activation energy, often found with oxides in contact with air (cf. Schwarz, *Proc. Phys. Soc.*, 1949, **62**, *A*, 530).] The powdered zinc oxide, being formed at a high temperature, is in a well-defined crystalline state and may be expected to be relatively free from strains, defects, and lattice vacancies, but the zinc oxide film growing on the oxidising metal will have a less perfect structure and will moreover have a high concentration of Zn_i diffusing out from the metal–oxide interface. In the latter case we suggest that (4) is followed at once by:

$$Zn_i^{2+} \longrightarrow Zn_l^{2+} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

an $O_{(ads)}^-$ also picking up a second electron, either from the conduction band of the oxide or from a second Zn_i, and moving into place as O_l^{2-} where the suffix l refers to an ion in its proper lattice position.

We have made similar observations upon the oxidation of copper to cuprous oxide at relatively low temperatures. Copper was prepared by reducing "AnalaR" copper sulphate solution with hot ammoniacal hydrazine, followed by filtration and thorough washing. The metal was subjected to four cycles of alternate oxidation and reduction as described by Garner, Stone, and Tiley (*Proc. Roy. Soc.*, 1952, *A*, **211**, 472) and finally oxidised to a thickness of *ca.* 150 Å by means of normal oxygen. The oxidation process was then followed at temperatures from 50° to 110° C and initial oxygen pressures of 1—3 cm., the non-equilibrated enriched oxygen being used, in a constant-volume apparatus. In no case was either equilibration or exchange observed. The oxidation followed the law

$$p_t/p_0 = \exp(-kt) \text{ or } -dp_t/dt = kp_t \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

as found by Wilkins and Rideal (*Proc. Roy. Soc.*, 1930, *A*, **128**, 394, 407) under similar conditions at temperatures from 142° to 242°, using copper strip, but our apparent activation energy was 15·5 kcal. mole^{-1}, in contrast to their value of 9·5 kcal. mole^{-1}; Garner, Stone and Tiley (*loc. cit.*) quote a value of possibly 7 kcal. mole^{-1} for the activation energy for adsorption of oxygen upon cuprous oxide films at about room temperature. Castellan and Moore (*J. Chem. Phys.*, 1949, **17**, 41) found a value of 38 kcal. mole^{-1} for the diffusion of vacancies through the bulk oxide lattice at temperatures around 900° c. Other literature values (in kcal. mole^{-1}) for the oxidation of copper include: Krup and Jasczcz (*Mét. Z.*, 1935, **2**, 329) 20·3, from 750° to 1070°; Gulbransen (*Trans. Electrochem. Soc.*, 1943, **83**, preprint, from *Chem. Abs.*, 1943, **37**, 2251) 24·9; Dravnieks (*J. Amer. Chem. Soc.*, 1950, **72**, 3761) ~35, from observations at 600° and 690°.

We conclude that, at least under our conditions, the dissociative adsorption of oxygen upon cuprous oxide is irreversible and is brought about by a mechanism such as that suggested by Garner, Stone, and Tiley (*loc. cit.*), *viz.*,

$$O_{2(g)} + 2Cu_i^{+} \longrightarrow 2O_{(ads)}^{-} + 2Cu^{2+} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Reaction (7) is then followed rapidly by the other changes necessary to incorporate $O_{(ads)}^{-}$ into the lattice—the movement of Cu^{+} ions from surface or sub-surface layers into place in proper lattice positions around the $O_{(ads)}^{-}$, the loss of one positive charge by the Cu^{2+}, the gain of an electron by $O_{(ads)}^{-}$, and the formation of two positive holes per O atom, which diffuse to the metal–oxide interface, where they are destroyed. It is possible that in our experiments (7) is the rate-determining step in the oxidation; an apparent activation energy of 15·5 kcal. mole^{-1} may not be unreasonable in view of the figure of 22 kcal. mole^{-1} found by us for the analogous reaction (4) on zinc oxide. The different activation energies recorded by various workers, mentioned above, for what may be the same process, may reflect differences in preparation of the oxide or in experimental conditions (cf. Gwathmey and Benton, *J. Chem. Phys.*, 1940, **8**, 431; *J. Phys. Chem.*, 1942, **46**, 969; Bénard and Talbot, *Compt. rend.*, 1946, **222**, 796): in addition, at low temperatures the reaction may be complicated by formation of nuclei of cupric oxide.

A more detailed study of the above and allied matters is in progress and will be reported elsewhere.

1, Wheeleys Road, Birmingham, 15. [*Received, April 28th*, 1954.]

The Components of Wool Wax. Part II. Synthesis of the Acids and Alcohols of the* iso- *and the* (+)-anteiso-*Series.*

By A. H. Milburn and E. V. Truter.

[Reprint Order No. 5348.]

Acids of the *iso*-series (12 members up to C_{28}) and of the optically active (+)-*anteiso*-series (13 members up to C_{31}) have been prepared by anodic syntheses. These have been reduced to the corresponding alcohols, and derivatives of the acids and the alcohols have been prepared.

Extended distillation of the methyl esters of the acidic fraction of wool wax has revealed the presence of no less than thirty-two acids, all containing more than 8 carbon atoms (Weitkamp, *J. Amer. Chem. Soc.*, 1945, **67**, 447). These fall into four groups: normal, α-hydroxy-, *iso*- (terminal *iso*-propyl group) and *anteiso*-acids (terminal CHMeEt group). Identification of the branched-chain acids is based on a special mixed-melting-point analysis, by which it is possible to locate the position at which the carbon chain branches, and on physical measurements which indicate that the series are homologous. Several

* Part I, *J.*, 1952, 4628.

iso-acids have been synthesised but only in occasional instances is a synthetic *anteiso*-acid available for a direct comparison.

Four exactly parallel groups have been identified among the aliphatic alcohols of wool wax. Here, identification of the members of the two branched-chain series rest on oxidation to the corresponding acid and comparison with Weitkamp's data (Murray and Schoenfeld, *J. Amer. Oil Chem. Soc.*, 1952, **29**, 416). The syntheses recorded below provide material for a direct comparison of both the acids and the alcohols; in addition, several derivatives of each have been prepared in order to facilitate future reference.

In the *iso*-series the C_{14}, C_{16}, and C_{18} acids were synthesised by Fordyce and Johnson (*J. Amer. Chem. Soc.*, 1933, **55**, 3368) by the action of Grignard reagents on the ester acid chlorides of dicarboxylic acids, and subsequent reduction of the resultant keto-esters. Stenhagen and his collaborators (*Arkiv Kemi Min., Geol.*, 1945, **19**, *A*, No. 8; 1949, **26**, *A*, No. 19) synthesised the C_{14}, C_{16}, C_{18}, C_{24}, and C_{26} *iso*-acids by condensation of an ω-iodo-ester with the ester of a β-keto-*iso*-acid, followed by decarboxylation of the product and reduction of the resultant keto-acid to the *iso*-acid. Anodic coupling reactions have been used by Hougen, Ilse, Sutton, and Villiers (*J.*, 1953, 98) for the synthesis of the C_{10}, C_{12}, C_{14}, C_{18}, and C_{20} *iso*-acids. The three lowest members were also synthesised by an alternative route. Buu-Hoï (*Rec. Trav. chim.*, 1953, **72**, 84) prepared 14-methylpentadecanoic acid by condensing *iso*valeraldehyde with ethyl undec-10-enoate.

In the *anteiso*-series only two of the optically active acids and one corresponding alcohol have been prepared. English and Velick (*J. Biol. Chem.*, 1945, **160**, 473) synthesised (+)-14-methylhexadecanoic acid from natural (−)-2-methylbutanol. First, the chain was lengthened by three carbon atoms by reaction with allylmagnesium bromide. Hydrogen bromide was added on to the olefin, and this was treated, as a Grignard reagent, with methyl 9-oxononanoate. The product, methyl 9-hydroxy-14-methylhexadecanoate, was dehydrated, hydrogenated, and hydrolysed to yield the desired acid. Crombie and Harper (*J.*, 1950, 2685) prepared (+)-6-methyloctanoic acid by oxidation of the corresponding alcohol. Natural (−)-2-methylbutanol was the starting material, and this, after conversion into the Grignard reagent, was treated with 2 : 3-dichlorodihydrofuran. Alkaline ring scission of the product, followed by hydrogenation, yielded (+)-6-methyloctanol.

Two racemic acids (C_9 and C_{19}) have been synthesised by Cason and Prout (*J. Amer. Chem. Soc.*, 1944, **66**, 49) and five (C_{11}, C_{13}, C_{15}, C_{17}, and C_{21}) by Nunn (*J.*, 1951, 1740). The melting points of the racemic acids are consistently higher than those of the corresponding optically active acids. Attempts by Nunn to resolve the (±)-acids failed.

The method of preparation used here is the elegant cross-coupling anodic synthesis of Linstead and Weedon (*J.*, 1950, 3326, and subsequent papers). It gives a fairly high yield (about 30%) for compounds containing less than 22 carbon atoms and has the advantage that, by suitable choice of starting materials, the products of side reactions are easily separated. Electrolysis of a branched-chain acid with the half-ester of a dicarboxylic acid affords the ester of a longer, branched-chain acid together with a hydrocarbon and the ester of a dicarboxylic acid as unwanted by-products. By using an excess of the half-ester, wastage of the more valuable branched-chain acid in the side reactions can be considerably diminished.

In the *anteiso*-series the starting material was (−)-2-methylbutanol isolated by distillation from commercial amyl alcohol. For use in the electrode synthesis it was first necessary to lengthen the carbon chain in order to remove the methyl substituent from the α-position. In effect, therefore, the starting material was (+)-4-methylhexanoic acid, obtained by condensation of the bromide with ethyl malonate. The starting material for the *iso*-acid electrode syntheses was 4-methylpentanoic acid derived from *iso*amyl bromide *via* the nitrile.

The results presented here for the synthetic branched-chain alcohols are in complete agreement with the findings of Murray and Schoenfeld (*loc. cit.*) for the alcohols isolated from wool wax. Those for the natural and the synthetic acids are also in accord except in the case of (+)-16-methyloctadecanoic acid, for which the melting point observed for the synthetic acid is 1·5° higher than that recorded by either Weitkamp or Murray and Schoenfeld. For the amides there are differences exceeding 1° in three cases: 10-methyl-

undecanamide (2·3°), 18-methylnonadecanamide (2·1°), and (+)-10-methyldodecanamide (2·7°). For two other acids the melting points obtained by different workers are not entirely self-consistent :

	12-Methyltridecanoic acid	12-Methyltridecanoic amide	16-Methylheptadecanoic acid	16-Methylheptadecanoic amide
Fordyce and Johnson	50·0—50·3°	—	67·8—68·2°	—
Stenhagen *et al.*	53·3—53·6	107·8°	67·8—68·5	106·4—106·8°
Hougen *et al.*	53·3—53·6	108·1—108·3	69·5—69·7	107·8—107·9
Milburn and Truter	51·5—52·0	108·0—108·5	67·5—68·0	106·4—106·5
Natural acid (Weitkamp)	53·3	107·3	69·5	107·3

Notwithstanding these differences, the structural assignments made by Weitkamp for the branched-chain wool wax acids are undoubtedly correct.

Experimental

M. p.s are corrected.

Electrolytic Cell.—The cell consisted of a glass cylinder of 1 l. capacity, fitted with a cooling coil, a reflux condenser, and two platinum electrodes (4 × 2·5 cm.). The electrolytic solvent was methanol (sufficient to cover the electrodes, 200—300 ml.) containing a small amount of sodium methoxide (1—2% based on the free acid content). Electrolysis was carried out at 1—2·5 amp., and was discontinued when the solution had become slightly alkaline (pH 7·5 or more). During the reaction the current always fell owing to gradual deposition of insulating polymer on the electrodes.

Treatment of the Electrolysate.—The *iso*-acids up to 16-methylheptadecanoic and the *anteiso*-acids up to 12-methyltetradecanoic acid were worked up by method A. Acids containing a greater number of carbon atoms were worked up by method B.

Method A.—The reaction mixture was neutralised with acetic acid, and the methanol was distilled off. An ethereal solution of the residue was washed with water and with aqueous sodium carbonate, dried ($MgSO_4$), and distilled through a short column into its constituent fractions.

Method B.—After removal of the methanol from the reaction mixture, the lower-boiling hydrocarbons were separated, where possible, by vacuum-distillation. The residue was hydrolysed in a small volume of alcoholic potassium hydroxide (3·5N in 90% ethanol). On acidification with dilute hydrochloric acid the free acids were precipitated and were filtered off. Treatment of the solids with cold light petroleum (b. p. 60—80°) extracted the monobasic acid and any residual hydrocarbon, while the dicarboxylic acid remained insoluble. The former were separated by alternate crystallisation from ethyl formate and light petroleum.

Derivatives.—All derivatives were prepared by accepted methods. The alcohols were obtained by reduction with lithium aluminium hydride. Equivalent weights of the acids were determined by titration against alcoholic 0·1N-sodium hydroxide (phenolphthalein).

Half Esters.—Methyl hydrogen succinate was obtained by the addition of methanol to succinic anhydride. Methyl hydrogen adipate and methyl hydrogen sebacate were prepared by the half-esterification of the corresponding acids (Jones, *J. Amer. Chem. Soc.*, 1947, **69**, 2352). Partial saponification of the diester was used for the preparation of the half esters of azelaic and suberic acid (Walker, *J.*, 1892, **61**, 709) and hexadecane-1 : 16-dicarboxylic acid (Hunsdiecker and Hunsdiecker, *Ber.*, 1942, **75**, 291).

Syntheses in the iso-*Series.*

4-*Methylpentanoic Acid.*—Redistilled *iso*amyl bromide (b. p. 120—122°; 102 g.) was heated with an 80% alcoholic solution of potassium cyanide (45 g. in 250 ml.) under reflux for 16 hr. Potassium bromide was filtered off, and the nitrile in the filtrate was hydrolysed by heating it for 16 hr. with potassium hydroxide (45 g.). Subsequently most of the solvent was distilled off. Acidification of the residual solution resulted in the separation of the free acid as a separate phase which was removed; ethereal extraction of the aqueous layer gave a further small amount of acid. The extract and the acid were combined, washed with water, and dried ($MgSO_4$), and the ether distilled off, to give 4-methylpentanoic acid (56 g.), b. p. 102—104°/13 mm. Similar yields were obtained in preparations on a larger scale.

4-*Methylpentanol.*—Over a period of 45 min. sodium (207 g.) was slowly added to a boiling

solution of ethyl 4-methylpentanoate (144 g.) in absolute ethanol (1800 ml.). After all the sodium had dissolved the mixture was diluted with water (700 ml.), the bulk of the ethanol was distilled off, and the residue was extracted with ether. The extract was washed and dried and the ether distilled off, to give 4-methylpentanol (74·5 g.), b. p. 152°.

1-*Bromo-4-methylpentane*.—4-Methylpentanol was refluxed for 3 hr. with 48% hydrobromic acid (152 g.) and sulphuric acid (82 g.). The products were distilled off, and the lower layer of the distillate was washed successively with water, concentrated hydrochloric acid, water, aqueous sodium carbonate, and water, and then dried ($MgSO_4$) and again distilled, to give 1-bromo-4-methylpentane (104 g.), b. p. 144—146°.

6-*Methylheptanoic Acid*.—During 90 min. 1-bromo-4-methylpentane (220 g.) was added to a hot solution of ethyl sodiomalonate (246 g.) in ethanol (800 ml.), and the mixture was heated under reflux for a further 2 hr. The bulk of the ethanol was then distilled off, potassium hydroxide in water (200 g. in 300 ml.) was added, and the mixture heated for 2 hr. The ethanol formed in the hydrolysis was distilled off and the residue refluxed for 3·5 hr. with sulphuric acid diluted with water (174 + 450 ml.). The mixture separated into two layers; the upper was drawn off, and the aqueous layer was extracted with ether. The extract was combined with the upper layer, and the solution was washed with water, dried ($MgSO_4$), and distilled, to give 6-methylheptanoic acid (144 g.), b. p. 128—129°/15 mm. (Found: equiv., 145. Calc.: equiv., 144) [amide, m. p. 114·3—114·6°; p-*bromophenacyl* ester, m. p. 67·7° (Found: C, 56·4; H, 6·0. $C_{16}H_{21}O_3Br$ requires C, 56·3; H, 6·2%)].

6-Methylheptanol had b. p. 187°/760 mm., n_D^{20} 1·4268, and gave a 3 : 5-*dinitrobenzoate*, m. p. 57·2—57·4° (Found: C, 55·9; H, 6·5. $C_{15}H_{20}O_6N_2$ requires C, 55·55; H, 6·2%), and *phenylurethane*, m. p. 80·7—81·0° (Found: C, 72·3; H, 9·0. $C_{15}H_{23}O_2N$ requires C, 72·3; H, 9·2%).

8-*Methylnonanoic Acid*.—4-Methylpentanoic acid (76·5 g.) and methyl hydrogen adipate (52·5 g., 0·5 mol.) were electrolysed and worked up in the manner outlined above, to give 8-methylnonanoic acid (28%), m. p. 19·0° (Found: equiv., 174. Calc.: equiv., 172). It gave a p-*bromophenacyl* ester, m. p. 67·4—68·0° (Found: Br, 22·0. $C_{18}H_{25}O_3Br$ requires Br, 21·6%), *benziminazole* derivative, m. p. 155·8—156·3° (Found: N, 12·0. $C_{16}H_{24}N_2$ requires N, 11·5%), amide, m. p. 103·0° (Weitkamp reports 103·1°), and *anilide*, m. p. 88·9—90·3° (Found: C, 77·4; H, 10·05. $C_{16}H_{25}ON$ requires C, 77·7; H, 10·1%).

8-Methylnonanol, b. p. 110—111°/11·5 mm., n_D^{20} 1·4352, gave a *phenylurethane*, m. p. 51·9—52·1° (Found: N, 5·3. $C_{17}H_{27}O_2N$ requires N, 5·05%), and a 3 : 5-*dinitrobenzoate*, m. p. 59·6° (Found: C, 57·9; H, 6·7. $C_{17}H_{24}O_6N_2$ requires C, 57·95; H, 6·9%).

10-*Methylundecanoic Acid*.—3-Methylbutyric acid (115 g.) and methyl hydrogen azelate (122 g.) gave 10-methylundecanoic acid (26%), m. p. 41·0° (Found: equiv., 199. Calc.: equiv., 200); Hougen *et al.* give 41·4—41·5°; Weitkamp reports 41·2°. Its amide had m. p. 105·7° (Hougen *et al.* give 108·1—108·4°; Weitkamp reports 108·0°) (Found: N, 7·2. Calc. for $C_{12}H_{25}ON$: N, 7·0%), its *anilide* m. p. 64·5—64·8° (Found: C, 78·4; H, 10·3. $C_{18}H_{29}ON$ requires C, 78·5; H, 10·6%), and its p-*bromophenacyl* ester, m. p. 69·7—70·3° (Found: Br, 22·0. $C_{20}H_{29}O_3Br$ requires Br, 21·65%).

10-*Methylundecanol*, b. p. 147—149°/18 mm., n_D^{20} 1·4412 (Found: C, 77·3; H, 14·1. $C_{12}H_{26}O$ requires C, 77·35; H, 14·1%), gave a 3 : 5-*dinitrobenzoate*, m. p. 57·5—57·8° (Found: C, 60·3; H, 7·5. $C_{19}H_{28}O_6N_2$ requires C, 60·0; H, 7·4%), and *phenylurethane*, m. p. 71·2—72·0° (Found: N, 4·6. $C_{19}H_{31}O_2N$ requires N, 4·6%).

12-*Methyltridecanoic Acid*.—4-Methylpentanoic acid (98 g.) and methyl hydrogen sebacate (183 g.) were electrolysed to give 12-methyltridecanoic acid (28·5%), m. p. 51·5—52·0° (Found: C, 73·3; H, 12·1. Calc. for $C_{14}H_{28}O_2$: C, 73·6; H, 12·35%), giving an amide, m. p. 108·0—108·5° (Found: N, 5·9. Calc. for $C_{14}H_{29}ON$: N, 6·15%), *anilide*, m. p. 75·1° (Found: C, 79·3; H, 10·8. $C_{20}H_{33}ON$ requires C, 79·2; H, 10·95%), and p-*bromophenacyl* ester, m. p. 71·5—72·0° (Found: Br, 18·75. $C_{22}H_{33}O_3Br$ requires Br, 18·8%).

12-*Methyltridecanol*, b. p. 161—163°/11 mm., m. p. 16·0°, n_D^{20} 1·4464 (Found: 78·6; H, 13·9. $C_{14}H_{30}O$ requires C, 78·4; H, 14·1%), gave a 3 : 5-*dinitrobenzoate*, m. p. 62·2—63·0° (Found: N, 7·2. $C_{21}H_{32}O_6N_2$ requires N, 6·9%), and *phenylurethane*, m. p. 66·5—67·0° (Found: N, 4·35. $C_{21}H_{35}O_2N$ requires N, 4·2%).

14-*Methylpentadecanoic Acid*.—6-Methylheptanoic acid (86 g.) was electrolysed together with methyl hydrogen sebacate (129·6 g.) to give 14-methylpentadecanoic acid (29%), m. p. 61·4—62·0° (Found: C, 75·1; H, 12·3. Calc. for $C_{16}H_{32}O_2$: C, 74·95; H, 12·6%). Weitkamp reports 62·4°. For the synthetic acid Fordyce *et al.* report 61·8—62·4°, and Stenhagen *et al.* 61·6°. The acid gave a *benziminazole* derivative, m. p. 101·0—101·5° (Found: N, 8·6. $C_{22}H_{36}N_2$ requires N, 8·5%), amide, m. p. 102·8° (Weitkamp reports 102·1°; Stenhagen *et al.*

report 101·4—101·7°) (Found : N, 5·7. Calc. for $C_{16}H_{33}ON$: N, 5·5%), *anilide*, m. p. 82·0—82·2° (Found : C, 79·5; H, 11·05. $C_{22}H_{37}ON$ requires C, 79·7; H, 11·2%), and *p*-bromophenacyl ester, m. p. 76·6—77·1°.

14-Methylpentadecanol, m. p. 30·0° (Stenhagen *et al.* report 29·4—30·4°) (Found : C, 79·3; H, 14·05. Calc. for $C_{16}H_{34}O$: C, 79·25; H, 14·15%), gave a 3 : 5-*dinitrobenzoate*, m. p. 67·0—67·3° (Found : C, 63·3; H, 8·25. $C_{23}H_{36}O_6N_2$ requires C, 63·3; H, 8·3%), and a *phenylurethane*, m. p. 73·3—73·8° (Found : C, 76·8; H, 10·7. $C_{23}H_{39}O_2N$ requires C, 76·4; H, 10·9%).

16-*Methylheptadecanoic Acid*.—8-Methylnonanoic acid (52 g.) and methyl hydrogen sebacate (86 g.) were electrolysed and worked up, to give 16-methylheptadecanoic acid (22%), m. p. 67·5—68·0° (Found : equiv., 287. Calc. : equiv., 284). The benziminazole derivative had m. p. 98·0—98·5°, the amide, m. p. 106·4—106·5°, the *anilide* m. p. 87·0—87·3° (Found : C, 80·2; H, 11·35. $C_{24}H_{41}ON$ requires C, 80·15; H, 11·5%), and the p-*bromophenacyl* ester, m. p. 79·7—80·0° (Found : Br, 16·9. $C_{26}H_{41}O_3Br$ requires Br, 16·6%).

16-Methylheptadecanol, m. p. 41·8—42·0° (Stenhagen *et al.* report 40·1—40·3°) (Found : C, 79·9; H, 14·3. Calc. for $C_{18}H_{38}O$: C, 79·9; H, 14·15%), gave a 3 : 5-*dinitrobenzoate*, m. p. 64·5—65·0° (Found : C, 65·0; H, 9·0. $C_{25}H_{40}O_6N_2$ requires C, 64·6; H, 8·7%), and a *phenylurethane*, m. p. 79·7° (Found : N, 3·4. $C_{25}H_{43}O_2N$ requires N, 3·6%).

18-*Methylnonadecanoic Acid*.—Electrolysis of 10-methylundecanoic acid (10 g.) and methyl hydrogen sebacate (10·8 g.) afforded 18-methylnonadecanoic acid (6·4%), m. p. 74·6—75·1° (Hougen *et al.* report 73·3—73·6°; Weitkamp gives 75·3°; Murray *et al.* give 75·0°) (Found : equiv., 314. Calc. : equiv., 312), which gave an amide, m. p. 103·0° (Hougen *et al.* give 105·9—106·1°; Weitkamp reports 105·1°) (Found : C, 77·0; H, 13·3. Calc. for $C_{20}H_{41}ON$: C, 77·2; H, 13·2%), *anilide*, m. p. 88·4—88·6° (Found : C, 80·7; H, 11·6. $C_{26}H_{45}ON$ requires C, 80·6; H, 11·7%), and p-*bromophenacyl* ester, m. p. 80·5—80·9° (Found : C, 66·0; H, 8·6. $C_{28}H_{45}O_3Br$ requires C, 66·0; H, 8·9%).

18-*Methylnonadecanol*, m. p. 49·8° (Murray *et al.* report 50·3° for the natural product) (Found : C, 80·3; H, 13·9. $C_{20}H_{42}O$ requires C, 80·45; H, 14·2%), gave a 3 : 5-dinitrobenzoate, m. p. 70·0—70·5°, and *phenylurethane*, m. p. 83·7—84·1° (Found : C, 78·0; H, 11·2. $C_{27}H_{47}O_2N$ requires C, 77·65; H, 11·35%).

20-*Methylheneicosanoic Acid*.—12-Methyltridecanoic acid (45 g.) was electrolysed with methyl hydrogen sebacate (86 g.) to give 20-methylheneicosanoic acid (28%), m. p. 79·1—79·5° (Weitkamp gives 79·4°; Murray *et al.* give 80·2°) (Found : equiv., 344. Calc. : equiv., 340). The *benziminazole* derivative had m. p. 90·9—91·5° (Found : N, 6·8. $C_{28}H_{48}N_2$ requires N, 6·8%), the *amide* m. p. 108·0—108·5° (Weitkamp gives 108·4°) (Found : C, 77·9; H, 13·1. $C_{22}H_{45}ON$ requires C, 77·8; H, 13·4%), and the p-*bromophenacyl* ester m. p. 83·7—84·2° (Found : C, 67·2; H, 8·8. $C_{30}H_{49}O_3Br$ requires C, 67·0; H, 9·2%).

20-*Methylheneicosanol*, m. p. 56·8—57·2° (Murray and Schoenfeld give 57·1°) (Found : C, 80·7; H, 13·8. $C_{22}H_{46}O$ requires C, 80·9; H, 14·2%), gave a 3 : 5-*dinitrobenzoate*, m. p. 74·4—74·8° (Found : C, 67·0; H, 9·3. $C_{29}H_{48}O_6N_2$ requires C, 66·9; H, 9·3%), and a *phenylurethane*, m. p. 86·3—86·7° (Found : N, 3·3. $C_{29}H_{51}O_2N$ requires N, 3·15%).

22-*Methyltricosanoic Acid*.—14-Methylpentadecanoic acid (12·8 g.) and methyl hydrogen sebacate (12·2 g.) were electrolysed to give 22-methyltricosanoic acid, m. p. 82·7—83·2° (Found : equiv., 367. Calc. : equiv., 368). Weitkamp gives 83·1°; Murray *et al.* give 83·4°. For the synthetic acid Stenhagen *et al.* give 83·1—83·5°. It gave an amide, m. p. 110·5—110·8° (Weitkamp reports 110·5°), *anilide*, m. p. 90·9—91·4° (Found : C, 80·5; H, 12·0. $C_{30}H_{53}ON$ requires C, 81·2; H, 12·05%), and *p*-bromophenacyl ester, m. p. 84·5—85·2°.

22-Methyltricosanol, m. p. 62·0—62·4° (Murray and Schoenfeld give 62·4°), gave a 3 : 5-*dinitrobenzoate*, m. p. 76·2—76·5° (Found : C, 68·05; H, 9·6. $C_{31}H_{52}O_6N_2$ requires C, 67·85; H, 9·55%), and a *phenylurethane*, m. p. 88·9—89·2° (Found : C, 79·2; H, 11·5. $C_{31}H_{55}O_2N$ requires C, 78·6; H, 11·7%).

24-*Methylpentacosanoic Acid*.—Electrolysis of 16-methylheptadecanoic acid (8 g.) and methyl hydrogen sebacate (12·2 g.) afforded 24-methylpentacosanoic acid (10%), m. p. 86·8—87·2°; Weitkamp gives 86·9°; Murray *et al.* give 86·3°. For the synthetic acid Stenhagen *et al.* report 86·4—86·7°. It gave an amide, m. p. 112·3—112·5° (Weitkamp gives 112·1°), anilide, m. p. 89·4—89·6°, and *p*-bromophenacyl ester, m. p. 81·1—81·6°.

24-Methylpentacosanol, m. p. 67·0—67·2° (Murray and Schoenfeld give 67·2°), gave a *phenylurethane*, m. p. 89·7—90·2° (Found : C, 78·9; H, 11·9. $C_{33}H_{59}O_2N$ requires C, 79·1; H, 11·8%).

26-*Methylheptacosanoic Acid*.—10-Methylundecanoic acid (2 g.) and methyl hydrogen hexadecane-1 : 16-dicarboxylate (3·3 g.) were electrolysed in the usual way. The electrolysis was

stopped after 150 hr. although the solution was still acid. After removal of the methanol and the hydrocarbon by distillation, the residue was hydrolysed and the free acids were extracted. The acids were neutralised precisely, and 0·1N-hydrochloric acid was then added in an amount calculated to liberate only the monocarboxylic acid. After extraction with ether and recrystallisation from ethyl acetate it had m. p. 88·8—89·0° (Weitkamp gives 89·3°) (Found: equiv., 430. Calc.: equiv., 424) (yield: 50 mg.) (*p*-bromophenacyl ester, m. p. 83·3—83·6°).

26-Methylheptacosanol, m. p. 72·0—72·4°, gave a phenylurethane, m. p. 90·5—90·8°.

Syntheses in the (+)-anteiso-*Series.*

Isolation of (−)-2-*Methylbutanol from Fusel Oil.*—Fusel oil containing 15—20% of optically active amyl alcohol was distilled at atmospheric pressure, through a 22″ electrically-jacketed column packed with wire-gauze rings. The take-off rate was 1·5 ml./hr. and the reflux ratio was 75 : 1. Four or five distillations through the column were required in order to obtain alcohol of the desired purity. The (−)-2-methylbutanol finally obtained had α_D −4·75° (l = 1) and was 99% pure. Optically pure amyl alcohol has α_D −4·81° (l = 1) (Couteur, Kenyon, and Rohan, *J. Appl. Chem.*, 1951, **1**, 341).

(+)-1-*Bromo*-2-*methylbutane.*—Phosphorus tribromide (227 g.) was added slowly to an efficiently stirred solution of (−)-2-methylbutanol (184 g.) in pyridine (57 g.) at 0°. The crude product was distilled off at 100 mm., dissolved in light petroleum (b. p. 40—60°), and washed successively with 5% aqueous sodium hydroxide, 10% sulphuric acid, concentrated sulphuric acid, and water. The solution was dried and distilled, to give (+)-2-methylbutyl bromide (202 g.), b. p. 119—121°, n_D^{20} 1·4450, α_D +4·75° (l = 1).

(+)-3-*Methylpentanoic Acid.*—1-Bromo-2-methylbutane (75·5 g.) was heated under reflux for 20 hr. with a solution of potassium cyanide (35 g.) in 80% ethanol (250 ml.). After the potassium bromide had been filtered off, the filtrate containing the nitrile was heated for a further 20 hr. with potassium hydroxide (40 g.). The solution was then worked up as described for 4-methylpentanoic acid, to give (+)-3-methylpentanoic acid (40·5 g.), b. p. 100—103°/12·5 mm.

(+)-4-*Methylhexanoic Acid.*—During 2 hr. optically active amyl bromide (202 g.) was added to an efficiently stirred, hot solution of ethyl sodiomalonate (251 g.) in absolute ethanol (900 ml.). After the mixture had been heated for a further 2 hr. some of the solvent (400 ml.) was distilled off, and the residue treated with aqueous potassium hydroxide (307 g. in 300 ml.) for 4 hr. under reflux. The alcohol was distilled off and the residue was heated under reflux for 4·5 hr. with a strong solution of sulphuric acid (272 ml. of H_2SO_4 in 600 ml. of H_2O). After cooling, the solution was extracted with ether, and the ethereal solution was washed, dried, and distilled, to give (+)-4-*methylhexanoic acid* (128 g.), b. p. 104—107°, n_D^{20} 1·4248, $[\alpha]_D^{20}$ +10·65° (10% in $CHCl_3$) (Found: C, 65·0; H, 11·1%; equiv., 130. $C_7H_{14}O_2$ requires C, 64·7; H, 10·8%; equiv., 130). The acid gave a *p*-bromophenacyl ester, m. p. 49·6—49·8°.

(+)-4-*Methylhexanol* had b. p. 172°, n_D^{20} 1·4256 (Found: C, 72·1; H, 13·8. $C_7H_{16}O$ requires C, 72·4; H, 13·8%).

(+)-6-*Methyloctanoic Acid.*—4-Methylhexanoic acid (117 g.) and methyl hydrogen succinate (231 g.) were electrolysed, to give 6-methyloctanoic acid (20%), b. p. 136—138°/10 mm., $[\alpha]_D^{20}$ +9·08° (10% in $CHCl_3$) (Found: equiv., 157. Calc.: equiv., 158). The amide had m. p. 89·7—90·1° (Weitkamp gives 89·7°; Crombie and Harper give 90—91°), and the p-*bromophenacyl* ester m. p. 59·0—59·3° (Found: Br, 23·0. $C_{17}H_{23}O_3Br$ requires Br, 22·5%).

6-Methyloctanol, b. p. 204—208°, $[\alpha]_D^{20}$ +9·80° (10% in $CHCl_3$), n_D^{20} 1·4360 (Found: C, 75·0; H, 13·8. Calc. for $C_9H_{20}O$: C, 75·0; H, 14·0%), gave a *phenylurethane*, m. p. 52·5—53·0° (Found: C, 73·0; H, 9·5. $C_{16}H_{25}O_2N$ requires C, 73·0; H, 9·6%).

(+)-8-*Methyldecanoic Acid.*—4-Methylhexanoic acid (117 g.) and methyl hydrogen adipate (192 g.) were electrolysed, to give 8-*methyldecanoic acid* (25%), b. p. 154—156°/10 mm., $[\alpha]_D^{20}$ +7·00° (10% in $CHCl_3$) (Found: equiv., 185. Reqd.: equiv., 186), which yielded an amide, m. p. 86·9° (Weitkamp gives 87·1°), *anilide*, m. p. 76·6—77·1° (Found: C, 78·1; H, 10·45. $C_{17}H_{27}ON$ requires C, 78·1; H, 10·4%), and p-*bromophenacyl* ester, m. p. 49·6—50·1° (Found: C, 59·7; H, 7·0. $C_{19}H_{27}O_3Br$ requires C, 59·5; H, 7·1%).

8-*Methyldecanol*, b. p. 234—238°/760 mm., $[\alpha]_D^{20}$ +8·64° (10% in $CHCl_3$), n_D^{20} 1·4402 (Found: C, 76·5; H, 13·8. $C_{11}H_{24}O$ requires C, 76·7; H, 14·05%), gave a *phenylurethane*, m. p. 46·5—46·8° (Found: C, 74·0; H, 9·9. $C_{18}H_{29}O_2N$ requires C, 74·2; H, 10·05%).

(+)-10-*Methyldodecanoic Acid.*—Electrolysis of a mixture of 3-methylpentanoic acid (42·5 g.)

and methyl hydrogen azelate (145 g.) gave 10-methyldodecanoic acid (34%), b. p. 172—176°/10 mm., m. p. 5·8° (Weitkamp gives 6·2°), $[\alpha]_D^{20}$ +5·88° (10% in $CHCl_3$) (Found: equiv., 219. Calc.: equiv., 214) [benziminazole derivative, m. p. 99·5—99·8°; *amide*, m. p. 89·5—90·0° (Weitkamp gives 92·5°) (Found: C, 73·0; H, 12·45. $C_{13}H_{27}ON$ requires C, 73·2; H, 12·7%); p-*bromophenacyl* ester, m. p. 55·5—56·0° (Found: C, 61·0; H, 7·3. $C_{21}H_{31}O_3Br$ requires C, 61·3; H, 7·6%)].

(+)-10-*Methyldodecanol*, b. p. 145—150/15 mm., n_D^{20} 1·4450, $[\alpha]_D^{20}$ +7·29° (Found: C, 77·6; H, 14·0. $C_{13}H_{28}O$ requires C, 77·9; H, 14·1%), gave a *phenylurethane*, m. p. 53·0—53·5° (Found: C, 75·0; H, 10·25. $C_{20}H_{33}O_2N$ requires C, 75·2; H, 10·4%).

(+)-12-*Methyltetradecanoic Acid*.—4-Methylhexanoic acid (130 g.) and methyl hydrogen sebacate (216 g.) were electrolysed and worked up in the usual manner, to give 12-methyltetradecanoic acid (24%), m. p. 22·8° (Weitkamp gives 23·0°), $[\alpha]_D^{20}$ +5·04° (10% in $CHCl_3$) (Found: equiv., 242. Calc.: equiv., 242). This gave a benziminazole derivative, m. p. 119·5—120·0°, amide, m. p. 86·6° (Weitkamp gives 86·4°), *anilide*, m. p. 58·0—58·3° (Found: C, 79·5; H, 11·2. $C_{21}H_{35}ON$ requires C, 79·45; H, 11·1%), and p-*bromophenacyl* ester, m. p. 58·7—59·3° (Found: C, 63·0; H, 7·6. $C_{23}H_{35}O_3Br$ requires C, 62·9; H, 8·0%).

(+)-12-*Methyltetradecanol*, b. p. 170—175°/15 mm., $[\alpha]_D^{20}$ +6·50° (10% in $CHCl_3$), n_D^{20} 1·4493 (Found: C, 78·7; H, 14·15. $C_{15}H_{32}O$ requires C, 78·9; H, 14·1%), gave a 3:5-*dinitrobenzoate*, m. p. 43·3—43·7° (Found: C, 62·8; H, 8·1. $C_{22}H_{34}O_6N_2$ requires C, 62·55; H, 8·1%), and *phenylurethane*, m. p. 60·0—60·3° (Found: C, 76·05; H, 10·5. $C_{22}H_{37}O_2N$ requires C, 76·0; H, 10·7%).

(+)-14-*Methylhexadecanoic Acid*.—6-Methyloctanoic acid (20 g.) and methyl hydrogen sebacate (54 g.) were electrolysed, to give 14-methylhexadecanoic acid (45 g.), m. p. 36·0°, $[\alpha]_D^{20}$ +4·38° (10% in $CHCl_3$) (Found: equiv., 274. Calc.: equiv., 270). Weitkamp gives 36·8°; Murray *et al.* give 37·3°. For the optically active synthetic acid English and Velick give 36·0—36·8°. The benziminazole derivative had m. p. 95·9—96·4°, the amide, m. p. 90·9—91·1° (Weitkamp reports 90·9°), the *anilide*, m. p. 61·3—61·6° (Found: C, 79·3; H, 11·2. $C_{23}H_{39}ON$ requires C, 79·95; H, 11·4%), and the p-*bromophenacyl* ester, m. p. 63·7—64·2° (Found: C, 64·4; H, 8·45. $C_{25}H_{39}O_3Br$ requires C, 64·4; H, 8·4%).

(+)-14-*Methylhexadecanol* had m. p. 18·5—19·0° (Murray and Schoenfeld give 18·4°), $[\alpha_D^{20}]$ +5·25° (10% in $CHCl_3$), n_D^{20} 1·4530 (Found: C, 79·7; H, 14·3. $C_{17}H_{36}O$ requires C, 79·6; H, 14·15%), its 3:5-*dinitrobenzoate* had m. p. 52·3—52·6° (Found: C, 64·0; H, 8·3. $C_{24}H_{38}O_6N_2$ requires C, 64·0; H, 8·5%), and its *phenylurethane* had m. p. 66·2—66·5° (Found: C, 77·0; H, 10·7. $C_{24}H_{41}O_2N$ requires 76·75; H, 11·0%).

(+)-16-*Methyloctadecanoic Acid*.—Electrolysis of 8-methyldecanoic acid (41 g.) and methyl hydrogen sebacate (47·5 g.) afforded 16-*methyloctadecanoic* acid (29%), m. p. 48·1—48·5° (Weitkamp gives 46·8°; Murray *et al.* give 46·0—46·3°), $[\alpha]_D^{20}$ +3·90° (10% in $CHCl_3$) (Found: C, 76·8; H, 12·7. $C_{19}H_{38}O_2$ requires C, 76·7; H, 12·7%). It gave an amide, m. p. 93·6° (Weitkamp reports 93·2°), *anilide*, m. p. 68·0—68·3° (Found: C, 80·1; H, 11·4. $C_{25}H_{43}ON$ requires C, 80·4; H, 11·6%), and p-*bromophenacyl* ester, m. p. 71·0—71·2° (Found: C, 65·3; H, 8·6. $C_{27}H_{43}O_3Br$ requires C, 65·45; H, 8·75%).

16-*Methyloctadecanol* had m. p. 30·4—30·7° (Murray and Schoenfeld give 27·5—31°), $[\alpha]_D^{20}$ +4·70° (10% in $CHCl_3$) (Found: C, 80·35; H, 14·05. $C_{19}H_{40}O$ requires C, 80·25; H, 14·15%), and gave a 3:5-*dinitrobenzoate*, m. p. 60·2—60·5° (Found: C, 65·6; H, 8·95. $C_{26}H_{42}O_6N_2$ requires C, 65·25; H, 8·85%), and *phenylurethane*, m. p. 73·4—73·7° (Found: C, 77·4; H, 11·3. $C_{26}H_{45}O_2N$ requires C, 77·4; H, 11·25%).

(+)-18-*Methyleicosanoic Acid*.—Electrolysis of a mixture of 10-methyldodecanoic acid (6 g.) and monomethyl sebacate (48·5 g.) gave 18-*methyleicosanoic acid* (200 mg.), m. p. 55·1—55·3° (Weitkamp gives 55·6°; Murray *et al.* give 55·8°), $[\alpha]_D^{20}$ +3·50° (10% in $CHCl_3$) (Found: equiv., 327. Reqd.: equiv., 326·5). It gave an amide, m. p. 94·4—94·6° (Weitkamp gives 94·1°), anilide, m. p. 73·8—74·1°, and p-*bromophenacyl* ester, m. p. 75·4—75·6° (Found: C, 66·3; H, 8·9. $C_{29}H_{47}O_3Br$ requires C, 66·5; H, 9·05%).

18-Methyleicosanol, m. p. 39·8—40·2° (Murray and Schoenfeld report 40·1°), $[\alpha]_D^{20}$ +4·30° (10% in $CHCl_3$), gave a 3:5-dinitrobenzoate, m. p. 64·1—64·3°, and a *phenylurethane*, m. p. 78·2—78·5° (Found: C, 77·8; H, 11·3. $C_{28}H_{49}O_2N$ requires C, 77·9; H, 11·45%).

(+)-20-*Methyldocosanoic Acid*.—A mixture of 12-methyltetradecanoic acid (29 g.) and methyl hydrogen sebacate (52 g.) was electrolysed, to give 20-*methyldocosanoic acid* (7 g.), m. p. 61·0—61·5° (both Weitkamp and Murray *et al.* give 62·1°), $[\alpha]_D^{20}$ +3·47° (Found: equiv., 357. Reqd.: equiv., 355), which afforded an amide, m. p. 99·0° (Weitkamp gives 99·9°), *anilide*, m. p. 79·2—79·4° (Found: C, 81·0; H, 12·0. $C_{29}H_{51}ON$ requires C, 81·05; H, 11·95%), and

p-*bromophenacyl* ester, m. p. 79·7—80·0° (Found: C, 67·5; H, 9·3. $C_{31}H_{51}O_3Br$ requires C, 67·5; H, 9·3%).

(+)-20-*Methyldocosanol*, m. p. 48·5—48·7° (Murray and Schoenfeld give 48·5°), $[\alpha]_D^{20}$ +3·53° (10% in $CHCl_3$) (Found: C, 81·2; H, 14·1. $C_{23}H_{48}O$ requires C, 81·1; H, 14·1%), gave a 3 : 5-dinitrobenzoate, m. p. 67·3—67·5°, and *phenylurethane*, m. p. 83·2—83·7° (Found: C, 78·4; H, 11·3. $C_{30}H_{53}O_2N$ requires C, 78·4; H, 11·6%).

(+)-22-*Methyltetracosanoic Acid*.—6-Methyloctanoic acid (1·2 g.) and monomethyl hexadecane-1 : 16-dicarboxylate (2·5 g.) were electrolysed and worked up as described for the C_{28} acid, to give 22-*methyltetracosanoic acid* (60 mg.), m. p. 67·5—67·8° (Weitkamp gives 67·8°; Murray *et al.* give 68·1°) (Found: C, 78·6; H, 13·0. $C_{25}H_{50}O_2$ requires C, 78·5; H, 13·1%) (*p*-bromphenacyl ester, m. p. 82·2—82·6°).

22-Methyltetracosanol had m. p. 54·0—54·5°; Murray and Schoenfeld give 54·6°.

(+)-24-*Methylhexacosanoic Acid*.—Electrolysis of 16-methyloctadecanoic acid (13 g.) and methyl hydrogen sebacate (28·3 g.) gave 24-methylhexacosanoic acid (150 mg.), m. p. 72·1° (Weitkamp gives 72·9°; Tiedt and Truter, *Chem. and Ind.*, 1952, 403, give 72·5°), $[\alpha]_D^{20}$ +2·64° (10% in $CHCl_3$) [amide, m. p. 104·7—104·9° (Weitkamp gives 104·5°)]; p-*bromophenacyl* ester, m. p. 86·4—86·7° (Found: C, 69·0; H, 10·0. $C_{35}H_{59}O_3Br$ requires C, 69·2; H, 9·7%).

24-Methylhexacosanol, m. p. 60·8° (Murray and Schoenfeld give 61·0°), $[\alpha]_D^{20}$ +3·40° (10% in $CHCl_3$), gave a *phenylurethane*, m. p. 87·0—87·4° (Found: C, 78·6; H, 11·6. $C_{34}H_{61}O_2N$ requires C, 79·15; H, 11·9%).

(+)-26-*Methyloctacosanoic Acid*.—20-Methyldocosanoic acid (6·0 g.) and methyl hydrogen suberate (3·4 g.) were electrolysed, to give 26-*methyloctacosanoic acid* (70 mg.), m. p. 76·2—76·5° (Tiedt and Truter give 76·1°) (Found: C, 79·8; H, 13·1. $C_{29}H_{58}O_2$ requires C, 79·5; H, 13·2%).

26-Methyloctacosanol had m. p. 65·0—65·3°.

(+)-28-*Methyltriacontanoic Acid*.—Electrolysis of a mixture of 20-methyldocosanoic acid (3 g.) and monomethyl sebacate (7·4 g.) gave 28-methyltriacontanoic acid (10%), m. p. 79·8—80·3° (Weitkamp gives 80·7°; Tiedt and Truter give 78·8°), $[\alpha]_D^{20}$ +2·43° (10% in $CHCl_3$) [amide, m. p. 107·0—107·3° (Weitkamp gives 107·0°; Tiedt and Truter give 107·6°)]; anilide, m. p. 92·2—92·6°; *p*-bromophenacyl ester, m. p. 85·9—86·4°.

(+)-28-*Methyltriacontanol* had m. p. 69·0—69·3°, $[\alpha]_D^{20}$ +3·06° (10% in $CHCl_3$) (Found: C, 82·15; H, 14·1. $C_{31}H_{64}O$ requires C, 82·2; H, 14·25%), and gave a 3 : 5-dinitrobenzoate, m. p. 81·2—81·5°, and a *phenylurethane*, m. p. 90·9—91·4° (Found: C, 79·8; H, 11·9. $C_{38}H_{69}O_2N$ requires C, 79·8; H, 12·15%).

The authors are indebted to Prof. J. B. Speakman for his interest and encouragement, and to the International Wool Secretariat for financial assistance.

TEXTILE CHEMISTRY LABORATORY, DEPT. OF TEXTILE INDUSTRIES,
UNIVERSITY OF LEEDS. [*Received, May 3rd*, 1954.]

Homolytic Aromatic Substitution. Part VII. Partial Rate Factors for the Phenylation of* tert.-*Butylbenzene and* p-*Di*-tert.-*butylbenzene.*

By J. I. G. Cadogan, D. H. Hey, and Gareth H. Williams.

[Reprint Order No. 5353.]

The proportions of the three isomeric *tert.*-butyldiphenyls formed in the phenylation of *tert.*-butylbenzene are determined by infra-red spectrometry. In addition, competitive experiments are carried out on the action of phenyl radicals derived from benzoyl peroxide on mixtures of *tert.*-butylbenzene and of *p*-di-*tert.*-butylbenzene with nitrobenzene. From these results the partial rate factors for the phenylation of *tert.*-butylbenzene and of *p*-di-*tert.*-butylbenzene are calculated. *tert.*-Butylbenzene provides the first example of over-all deactivation encountered in homolytic substitution and this is attributed to a marked steric effect on the *ortho*-positions. Homolytic substitution, while insensitive to the polar character of nuclear substituents, is nevertheless sensitive, as is electrophilic substitution, to steric influences. Synthetic work leading to the preparation of the three isomeric *tert.*-butyldiphenyls is also reported.

The partial rate factors for homolytic phenylation of nitrobenzene, the halogenobenzenes, and diphenyl have been reported in Parts I—V (Hey, Nechvatal, and Robinson, *J.*, 1951, 2892; Augood, Hey, and Williams, *J.*, 1952, 2094; 1953, 44; Augood, Cadogan, Hey, and Williams, *J.*, 1953, 3412; Cadogan, Hey, and Williams, *J.*, 1954, 794), and these and other results have been discussed by Hey and Williams (*Discuss. Faraday Soc.*, 1953, **14**, 216). In the present communication the survey of homolytic aromatic substitution is extended by the determination of partial rate factors for the phenylation of *tert.*-butylbenzene and *p*-di-*tert.*-butylbenzene with benzoyl peroxide. The phenylation of toluene, ethylbenzene, and *iso*propylbenzene will be reported in later papers.

Phenylation of the alkylbenzenes is complicated by the possibility of attack in the side chain (Augood, Hey, Nechvatal, Robinson, and Williams, *Research*, 1951, **4**, 386; Dannley and Zarensky, Amer. Chem. Soc. Abs., 124th Meeting, 1953, 36.0). In the reactions reported in this paper, however, no products derived from attack on the side chain by free radicals were isolated. This is not unexpected, because Kooyman (*Discuss. Faraday Soc.*, 1951, **10**, 163), in a comparison of the reactivities of the alkylbenzenes towards free trichloromethyl radicals based on the retardation of the addition of carbon tetrachloride to hexadecene, has shown that little or no retardation occurs with compounds such as benzene and *tert.*-butylbenzene, which do not contain α-methylenic hydrogen atoms. Gregg and Mayo (*Discuss. Faraday Soc.*, 1947, **2**, 328) came to similar conclusions after a study of the inhibition of the polymerisation of styrene by alkylbenzenes. The kinetics of the decomposition of benzoyl peroxide in *tert.*-butylbenzene have been investitated (Bartlett and Nozaki, *J. Amer. Chem. Soc.*, 1946, **68**, 1686; Hartmann, Sellers, and Turnbull, *ibid.*, 1947, **69**, 2416), but no attempt was made, in either case, to isolate any products of the reaction. The arylation of *p*-di-*tert.*-butylbenzene has not previously been studied.

The overall effect of the *tert.*-butyl group was measured by means of competitive experiments with nitrobenzene, which were conducted under conditions which reduced the importance of any possible side reactions such as the removal of the products by further phenylation. This was achieved by the use of a large excess of an equimolar mixture of the competing solvents compared with the source of the phenyl radicals. Under these conditions 90% of the benzoyl peroxide was accounted for in the experiments with *tert.*-butylbenzene and 77% in those with *p*-di-*tert.*-butylbenzene (see Experimental section). The hitherto unknown 2 : 5-di-*tert.*-butyldiphenyl was isolated from the products of the phenylation of the mixture of nitrobenzene and *p*-di-*tert.*-butylbenzene, thus showing that phenylation at a position *ortho* to the bulky *tert.*-butyl group does occur. The ratios of the isomerides produced in the phenylation of *tert.*-butylbenzene were measured by infra-

* Part VI, *J.*, 1954, 2747.

red spectroscopy, after synthetic work had been completed to obtain the three isomeric *tert.*-butyldiphenyls, two of which had not previously been described. 2-, 3-, and 4-*tert.*-Butyldiphenyl were obtained as the results of the decomposition in benzene of *o*- and *m*-*tert.*-butylbenzoyl peroxides and *p*-*tert.*-butyl-*N*-nitrosoacetanilide respectively.

In an attempt to prepare 2-*tert.*-butyldiphenyl it was observed that *o*-*tert.*-butyl-*N*-nitrosoacetanilide, on decomposition in benzene, gave (*a*) *tert.*-butylbenzene, (*b*) *o*-*tert.*-butylacetanilide, (*c*) diphenyl, and (*d*) an ester or mixture of esters believed to be the isomeric *tert.*-butylphenyl acetates. An intermediate in the preparation of 3-*tert.*-butyldiphenyl was *m*-*tert.*-butylbenzoic acid, which Crawford and Stewart (*J.*, 1952, 4443) obtained by deamination of 2-bromo-4-*tert.*-butylaniline to *m*-bromo-*tert.*-butylbenzene (b. p. 100°/40 mm.; 70%) followed by carboxylation of the Grignard reagent. In our hands the deamination step yielded *tert.*-butylbenzene (b. p. 100°/40 mm.; 48·5%), and *m*-bromo-*tert.*-butylbenzene (b. p. 108—110°/16 mm.; 37%), indicating that removal of a bromine atom from a position *ortho* to the diazonium group had taken place. It may be noted that, in the preparation of *o*-*tert.*-butylbenzoic acid, the deamination of 3-bromo-4-*tert.*-butylaniline revealed no such anomaly. *m*-*tert.*-Butylbenzoic acid was also prepared by a new route, by means of the von Richter reaction with alcoholic potassium cyanide and *tert.*-butyl-*p*-nitrobenzene, but the yield was too low to make the method of synthetic value.

Experimental methods and results

Determination of the Extent of Side-chain Attack in tert.-*Butylbenzene.*—The possible products of attack by phenyl or benzoyloxy-radicals on the side chain of *tert.*-butylbenzene were considered to be those derived from (*a*) abstraction of a β-hydrogen atom by the radical to give benzene and/or benzoic acid, together with the product derived from dimerisation of the fragment so produced, that is, 2 : 5-dimethyl-2 : 5-diphenylhexane, and (*b*) substitution of a β-hydrogen atom by a phenyl or benzoyloxy-radical to give 2-methyl-2 : 3-diphenylpropane or 2 : 2-dimethylphenethyl benzoate. The former product has the same molecular formula as the products of nuclear phenylation and its presence cannot, therefore, be detected by microanalysis for carbon and hydrogen.

Benzoyl peroxide (8 g.) was allowed to decompose in *tert.*-butylbenzene (150 ml.) in a thermostat at 80° for 72 hr. The fraction likely to contain the products of phenylation was isolated by the standard procedure described in Part II (*loc. cit.*). No benzene was isolated. The yield of phenylated product was 3·718 g. (b. p. 60—100°/0·1 mm.; n_D^{17} 1·5750) (Found: C, 91·3; H, 8·6. Calc. for $C_{16}H_{18}$: C, 91·4; H, 8·6%). This fraction, therefore, contained no dimer (Calc. for $C_{20}H_{26}$: C, 90·2; H, 9·8%). Quantitative infra-red analysis, as described below, of this and similar fractions obtained from other experiments, proved the absence of 2-methyl-2 : 3-diphenylpropane which, if it had been formed, would have been isolated with the products of nuclear phenylation. After removal of this fraction the high-boiling resin (1·2 g.) was purified by distillation and chromatographed on alumina (2 × 25 cm.) with benzene–light petroleum as eluant. This afforded irresolvable gums which were thought to be mixtures of the many possible *tert.*-butylterphenyls (Found: C, 91·3; H, 7·7. Calc. for $C_{22}H_{22}$: C, 92·3; H, 7·7%). Benzoic acid (3·40 g.; m. p. and mixed m. p. 118°) and diphenyl-4-carboxylic acid (0·2 g.; m. p. and mixed m. p. 224—225°) were also isolated. Thus, 86% of the benzoyl peroxide was accounted for and no products of side-chain attack were isolated or detected.

Direct Determination of $^{PhBu^t}_{PhNO_2}K$.—Benzoyl peroxide (6 g.) was added during 20 min. to an equimolar mixture (200 ml.) of *tert.*-butylbenzene and nitrobenzene maintained at 80° in a thermostat. The decomposition was considered to be complete after 72 hr. The mixture of diphenyls was isolated quantitatively and analysed by estimation of the nitro-compound by reduction with titanous chloride. The standard procedure described in Part II (*loc. cit.*) was employed. In the final distillation, fore-runs, *i.e.*, mixed fractions containing the last traces of nitrobenzene and the first traces of *tert.*-butyldiphenyls, were collected separately from the *tert.*-butyldiphenyl–nitrodiphenyl fraction, so that the latter should not be contaminated with the last traces of nitrobenzene. The fore-runs were analysed for nitrobenzene with titanous chloride, and a correction in terms of *tert.*-butyldiphenyl, found by difference, was applied to the composition of the *tert.*-butyldiphenyl–nitrodiphenyl fraction. In order to estimate the nitrobenzene content of the fore-runs, a slight modification of the procedure outlined in Part II became necessary in order to overcome loss of nitrobenzene by volatilisation during the estimation.

Carbon dioxide was passed through the mixture of buffer (30 ml.) and acetone (10 ml.; "AnalaR") for 15 min. The solution to be analysed was made up with acetone saturated with carbon dioxide, and 20 ml. were pipetted into the buffer–acetone mixture. Carbon dioxide was passed through the mixture for a further 10 min., the titanous chloride was then added, and the estimation completed as described for the nitrodiphenyls (Part II, *loc. cit.*).* A fraction taken immediately before the fore-run proved to consist entirely of nitrobenzene, showing that neither the fore-run nor the product fraction contained residual *tert.*-butylbenzene. It can be assumed that the fore-runs contained no nitrodiphenyls, since these were found not to distil until a temperature 60° above that at which the fore-runs were collected had been reached. The high-boiling residue left after completion of the distillation was of negligible weight. The results of these experiments (1—3) are given in Table 1. The weight of benzoic acid recorded is composed

TABLE 1.

Expt. No.	1	2	3
Diaryl fraction (g.)	3·389	3·444	3·302
$Ph{\cdot}C_6H_4{\cdot}NO_2$ (%)	84·00	83·63	86·79
Fore-run (g.)	1·333	0·814	1·852
$Ph{\cdot}NO_2$ in fore-run (%)	88·73	92·96	88·13
Bu^t-diphenyls in fore-run (g.)	0·150	0·058	0·220
Corr. wt. of diaryl fraction (g.)	3·539	3·502	3·522
$Ph{\cdot}C_6H_4{\cdot}NO_2$ corr. (%)	80·41	82·23	81·38
$^{PhBu^t}_{PhNO_2}K$	0·230	0·205	0·217
$Ph{\cdot}CO_2H$ (g.)	3·300	3·195	3·293
$(Ph{\cdot}CO_2)_2$ accounted for (%)	90·4	88·3	90·2

Hence $^{PhBu^t}_{PhNO_2}K = 0{\cdot}217$.

of that obtained from the saponification (0·12 mole per mole of benzoyl peroxide) and that formed in the free state (0·94 mole per mole of benzoyl peroxide).

Direct Determination of $^{p\text{-}Bu^t_2C_6H_4}_{PhNO_2}K$.—Experiments 4, 5, 6, and 7 were carried out with benzoyl peroxide (6 g.) in an equimolar mixture (200 g.) of nitrobenzene and *p*-di-*tert.*-butylbenzene. The reactions were allowed to proceed in a thermostat at 80° for 72 hr. The isolation and analysis of the mixed diphenyls were carried out by the standard procedure (Part II, *loc. cit.*). The fore-runs were analysed for nitrodiphenyl and the necessary correction applied to the composition of the di-*tert.*-butyldiphenyl–nitrodiphenyl fraction. A fraction taken immediately before the fore-run proved to consist entirely of *p*-di-*tert.*-butylbenzene. Again it can be assumed that the fore-runs contained no nitrobenzene or 2 : 5-di-*tert.*-butyldiphenyl. The high-boiling resin left after the distillation was of negligible weight. The results are given in Table 2. The amount of benzoyl peroxide accounted for is lower than in previous cases

TABLE 2.

Expt. No.	4	5	6	7
Diaryl fraction (g.)	2·635	1·805	2·550	2·657
$Ph{\cdot}C_6H_4{\cdot}NO_2$ (%)	82·09	79·73	82·43	81·93
Fore-run (g.)	0·422	0·245	0·868	0·588
$Ph{\cdot}C_6H_4{\cdot}NO_2$ in fore-run (%)	27·56	7·23	6·12	21·28
$Ph{\cdot}C_6H_4{\cdot}NO_2$ in fore-run (g.)	0·116	0·018	0·053	0·125
Corr. wt. of diaryl fraction (g.)	2·751	1·823	2·603	2·782
$Ph{\cdot}C_6H_4{\cdot}NO_2$ corr. (%)	82·85	79·98	82·79	82·74
$^{p\text{-}Bu^t_2C_6H_4}_{PhNO_2}K$	0·155	0·166	0·156	0·156
$Ph{\cdot}CO_2H$ (g.)	2·930	—	3·100	3·050
$(Ph{\cdot}CO_2)_2$ accounted for (%)	76·0	—	77·0	77·0

Hence $^{p\text{-}Bu^t_2C_6H_4}_{PhNO_2}K = 0{\cdot}158$.

(Parts II, III, and IV) because benzoic acid is lost in the distillation of the unchanged *p*-di-*tert.*-butylbenzene in the first stage of the working-up process. The weight of the diaryl fraction in experiment 5 is low because some of the homogeneous reaction mixture was accidentally lost on removal of the reaction flask from the thermostat. This will not alter the value of $^{p\text{-}Bu^t_2C_6H_4}_{PhNO_2}K$, which depends on the relative amounts of diaryls present and not on the total amount.

* This modification was also used in the estimation of nitrobenzene in the fore-runs obtained from experiments with nitrobenzene–bromobenzene and nitrobenzene–iodobenzene mixtures (Part IV, *loc. cit.*) but was not described therein.

Determination of the Ratio of Isomerides formed in the Phenylation of tert.*-Butylbenzene.*—Benzoyl peroxide was allowed to decompose in *tert.*-butylbenzene at 80° in a thermostat. The standard procedure described in Part II (*loc. cit.*) was used for the isolation of the *tert.*-butyldiphenyl fraction from the products of experiments 8, 9, and 10. The details of these experiments are given in Table 3.

TABLE 3.

Expt. no.	$(Ph\cdot CO_2)_2$ (g.)	PhBu^t (ml.)	Bu$^t\cdot C_6H_4\cdot Ph$ [mole/mole of $(Ph\cdot CO_2)_2$]	n_D^{17}	Found (%) C	H
8	8·00	130	0·53	1·5750	91·3	8·6
9	4·00	90	0·53	1·5750	91·4	8·4
10	4·00	90	0·52	1·5750	91·3	8·7

The composition of the three mixtures of isomeric *tert.*-butyldiphenyls, which had identical physical properties, was determined by an infra-red spectrographic method, using a Grubb-Parsons single-beam instrument with rock-salt optics and equipped with an automatic pen recorder. Examination of the spectra of 3-*tert.*-butyldiphenyl as a capillary film, and of 2- and 4-*tert.*-butyldiphenyl as crystalline powders in Nujol mulls between rock-salt plates, revealed that intense absorption bands occurred in the region 12—13 μ. The frequencies of these " key " bands were almost identical with those of the key bands exhibited by all other 2-, 3-, and 4-substituted diphenyls so far investigated by us (Parts III and IV, *loc. cit.*). The frequencies were: 2-*tert.*-butyldiphenyl 755, 779 cm.$^{-1}$; 3-*tert.*-butyldiphenyl 763, 803 cm.$^{-1}$; 4-*tert.*-butyldiphenyl 770, 842 cm.$^{-1}$. Calibration spectra of solutions in nitromethane of the pure isomerides were recorded in the frequency range 700—850 cm.$^{-1}$. The spectra of the three experimental mixtures 8, 9, and 10 in nitromethane, and the background spectrum of the solvent were then recorded. The same rock-salt cell of thickness 130 μ was used in each case. The determination is most accurate when the absorption at the key wave-length is about 60%. The concentrations of the solutions employed (g./5 ml.), which absorbed radiation to this extent at the key wave-lengths, were: 3-*tert.*-butyldiphenyl, 0·8320; 4-, 0·2923; and the experimental mixtures about 0·89. The compositions of the mixtures, calculated by the method outlined below, are given in Table 4.

TABLE 4. *Analysis of products obtained in the phenylation of* tert.*-butylbenzene.*

Expt. no.	Composition (%) 2-	3-	4-	Expt. no.	Composition (%) 2-	3-	4-
8	23	50	27	10	25	48	27
9	24	50	26	Mean	24	49	27

Calculation of the Ratio of Isomerides.—The method was based on that described in Part V (*loc. cit.*), which involved solution of equations of the type

$$\text{(at a given wave-length)} \quad \varepsilon_{\text{mixture}} = x\varepsilon_2 + y\varepsilon_3 + z\varepsilon_4 \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where x, y, and z are the fractions of the 2-, 3-, and 4-isomeride present in the mixture, and the ε terms, in this case, are not absolute values of the extinction coefficients (as in Part V) but involve a constant (cell thickness). The magnitudes of these extinction coefficients were obtained from the spectra of the standard solutions of the pure isomerides and the experimental mixtures. Measurements were made at the frequencies of the key bands of the 3- and the 4-isomeride (803, 842 cm.$^{-1}$). The key band of the 2-isomeride was not employed because it was too close to an intense band common to each isomeride, as in previous cases. It was observed that ε_2 was negligible at 803 and 842 cm.$^{-1}$ and hence could be neglected. Such transparency of a benzene derivative to infra-red radiation at the frequencies of the key absorption bands of its isomeric forms is not uncommon (Thompson, Torkington, and Whiffen, *Trans. Faraday Soc.*, 1945, **41**, 200).

The accuracy of the analysis was determined by two methods, both of which involve the analysis of artificial mixtures of known composition. Insufficient 2-*tert.*-butyldiphenyl was available for inclusion in these, so that synthetic mixtures, containing known weights of an experimental mixture with known amounts of 3- and 4-isomerides added, were made up in nitromethane. Presupposing that the experimental mixture included in this synthetic mixture had been correctly analysed, the composition of the synthetic mixture was known. An estimate of its composition was made from its spectrum by the standard method. Comparison of this " found " value with the known value for the composition then gave an estimate of the

reliability of the method. A further check was imposed by application of the principle of additivity of optical densities. In this way, the extinction coefficient, $\varepsilon_{mixt.}$, of any of the synthetic mixtures at any wave-length, can be predicted by substituting for y, z, ε_3 and ε_4 in equation 1, ε_2 being zero. Comparison of this predicted value for $\varepsilon_{mixt.}$ with that actually observed is a measure of the accuracy of the determination. The results of the accuracy determinations are given in Table 5. That the compositions of the mixtures and their optical densities can be predicted to within a few per cent., coupled with the observation that the spectra of the experimental mixtures contained absorption bands peculiar to the three isomerides only, is taken to be proof that the experimental mixtures isolated by our methods contained no extraneous products, and that the mean value for the composition of the mixtures presented in Table 4 is reliable to within a few per cent.

TABLE 5. *Infra-red analysis of synthetic mixtures of* tert.*-butyldiphenyls.*

Solution		Composition (%) 2-	3-	4-	$\varepsilon_{mixt.}$ 803 cm.$^{-1}$	842 cm.$^{-1}$
S_1 containing Expt. no. 8	Found	4·0	65·2	30·8	0·5217	0·5781
	Known	7·0	61·6	31·4	0·4854	0·5895
S_2 containing Expt. no. 9	Found	19·2	52·0	28·8	0·4128	0·5342
	Known	18·6	52·4	29·0	0·4160	0·5384
S_3	Found	0	70·6	29·6	0·5540	0·5592
	Known	0	70·1	29·9	0·5600	0·5560
S_4 containing Expt. no. 10	Found	18·5	53·1	28·3	0·4116	0·5265
	Known	20·8	50·8	28·4	0·4035	0·5269
S_5 containing Expt. no. 8	Found	15·0	45·3	39·7	0·3650	0·7401
	Known	14·7	45·3	40·0	0·3645	0·7299

Preparation of Reagents.—Unless otherwise stated, the light petroleum used had b. p. 60—80° and all solids were recrystallised to constant m. p.

Benzoyl peroxide (May & Baker) and nitrobenzene were purified according to the procedure described in Part II (*loc. cit.*), and nitromethane according to that described in Part IV (*loc. cit.*). *tert.*-Butylbenzene was prepared by the method of Kharasch and Brown (*J. Amer. Chem. Soc.*, 1939, **61**, 2142); the crude product was washed with concentrated sulphuric acid until the washings were colourless, then with aqueous sodium hydrogen carbonate, and with water, and dried ($CaCl_2$); pure *tert.*-butylbenzene was obtained after distillation from sodium through a 4-foot helix-packed column (b. p. 169°/760 mm., n_D^{20} 1·4927).

p-Di-*tert.*-butylbenzene was prepared by the Friedel–Crafts reaction from *tert.*-butyl chloride and *tert.*-butylbenzene. Freshly prepared *tert.*-butyl chloride (400 g.) was added dropwise during 3 hr. to a stirred mixture of anhydrous aluminium chloride (16 g.) and *tert.*-butylbenzene (800 ml.) at room temperature. Solid separated after 1½ hr. and stirring became difficult after the addition was complete, but was continued for ½ hr. The pale yellow semi-solid mass was homogenised by warming and poured slowly into vigorously agitated water, to give colourless needles (m. p. 73—76°), which were collected. After being pressed and washed with cold methanol (150 ml.), the product recrystallised from methanol in colourless needles (550 g.), m. p. 76—77°.

tert.-*Butyl*-o- *and* -p-*nitrobenzene*.—Nitration of *tert.*-butylbenzene (Brown and Nelson, *ibid.*, 1951, **73**, 5605) gave a mixture of isomeric *tert.*-butylnitrobenzenes in 96% yield. This was rectified by means of a 7-foot helix-packed column, and gave *tert.*-butyl-*o*-nitrobenzene (b. p. 128°/20 mm., n_D^{20} 1·5175; 14%), *tert.*-butyl-*p*-nitrobenzene (b. p. 152°/24 mm., n_D^{20} 1·5334, supercooled; 62%), and an intermediate fraction (b. p. 128—150°/20 mm.; 12%), which was discarded.

4-tert.-*Butyldiphenyl*.—Reduction of *tert.*-butyl-*p*-nitrobenzene by granulated tin and hydrochloric acid gave crude *p-tert.*-butylaniline (87%), which was converted into the acetyl derivative and recrystallised from benzene–light petroleum to constant m. p. (174°; colourless plates). The anilide (7·1 g.) so obtained was stirred with acetic acid (30 ml.), acetic anhydride (25 ml.), fused potassium acetate (5 g.), and phosphoric oxide (0·5 g.) at 0°, while nitrosyl chloride (3 g.) in acetic anhydride (15 g.) was added dropwise during 20 min. After a further 90 min. at 8°, the pale yellow solution was poured slowly into agitated iced water containing sufficient sodium hydrogen carbonate to neutralise the acetic acid. The yellow solid which separated was collected on a cooled filter and washed with iced water (100 ml.). The product (7·9 g.), m. p. 57·5° (decomp.), was dried at 0° in an evacuated desiccator containing potassium hydroxide and phosphoric oxide. *p-tert.*-Butyl-*N*-nitrosoacetanilide (7·9 g.) was dissolved at room temperature in dry benzene (400 ml.; "AnalaR") containing a suspension of anhydrous

sodium sulphate (15 g.) and sodium hydrogen carbonate (15 g.). Decomposition immediately commenced, as indicated by rapid evolution of gas and darkening. The red solution was stirred for 24 hr. and then boiled under reflux for a further 2 hr. Removal of benzene from the filtered solution left a dark red oil, which on distillation *in vacuo* gave a yellow solid (3·5 g.; b. p. 100°/0·15 mm., m. p. 49°). The product was purified by shaking its solution in benzene with successive portions (15 ml.) of concentrated sulphuric acid until both layers were colourless. The benzene solution was freed from acid, and evaporation of the solvent gave a white crystalline solid which, on recrystallisation from ethanol, gave 4-tert.-*butyldiphenyl* in colourless plates, m. p. 52·2° (corr.) (Found: C, 91·1; H, 8·7. $C_{16}H_{18}$ requires C, 91·4; H, 8·6%).

Preparation of m-*tert.-Butylbenzoic Acid.*—(i) *By the von Richter reaction* (cf. *Chem. Reviews*, 1951, **49**, 382). *tert.*-Butyl-*p*-nitrobenzene (14 g., 1 mol.) was heated for 3 hr. at 140° with crystalline potassium cyanide (60 g., 12 mol.) and ethylene glycol (250 ml., 90%). The resulting dark brown mixture was poured into water and basified with aqueous sodium hydroxide. The red emulsion which had formed was dispersed by ether-extraction, and the aqueous layer was acidified and steam-distilled. The distillate (4 l.) was extracted with ether (three times). Evaporation of the solvent gave a white solid (m. p. 124—126°), which on recrystallisation from 5% acetic acid gave *m-tert.*-butylbenzoic acid (0·7 g.), m. p. 128° (corr.). A mixed m. p. with a sample prepared by method (ii) below was 127° (Found: C, 74·1; H, 7·9. Calc. for $C_{11}H_{14}O_2$: C, 74·2; H, 7·9%). (ii) *By the method of Crawford and Stewart* (*loc. cit.*). *m*-Bromo-*tert.*-butylbenzene was prepared by the bromination of *p-tert.*-butylacetanilide by bromine in acetic acid followed by hydrolysis of the 2-bromo-4-*tert.*-butylacetanilide, m. p. 138°, to the amine. 2-Bromo-4-*tert.*-butylaniline hydrochloride (140 g.) was diazotised at 0° and 50% hypophosphorous acid (780 ml.) added dropwise to the stirred ice-cold solution. The mixture was kept at 0° for 24 hr., and the red oil which had separated was extracted with ether. The ether extracts were washed with 4N-potassium hydroxide solution (four times) and with water, and dried ($CaCl_2$). Distillation of the residue after removal of ether gave fractions: (i) b. p. 100°/40 mm., 70—82°/16 mm., 34·2 g., n_D^{20} 1·4940, (ii) b. p. 82—108°/16 mm., 1·2 g., n_D^{20} 1·5133, and (iii) b. p. 108—110°/16 mm., 41·7 g., n_D^{20} 1·5341. Fraction (i) contained no bromine and had n_D^{20} similar to that of *tert.*-butylbenzene (1·4927). It was converted into the *p*-sulphonamide which crystallised from ethanol in colourless needles, m. p. 137·5°, both alone and admixed with *p-tert.*-butylbenzenesulphonamide (Found: C, 56·1; H, 6·8. Calc. for $C_{10}H_{15}O_2NS$: C, 56·3; H, 7·1%). Fraction (iii) was converted into the Grignard reagent, carboxylation of which gave *m-tert.*-butylbenzoic acid (70%), which after recrystallisation from light petroleum had m. p. 127°. This reaction therefore gave *tert.*-butylbenzene (48·5%) in addition to the expected 3-bromo-*tert.*-butylbenzene (37%). Crawford and Stewart (*loc. cit.*) reported the isolation of only 3-bromo-*tert.*-butylbenzene, b. p. 100°/40 mm., in 70% yield.

m-tert.-*Butylbenzoyl Peroxide.*—*m-tert.*-Butylbenzoyl chloride, prepared from the acid (21·4 g.), was added dropwise during 3 hr. to a well-stirred ice-cold 10% solution of sodium hydroxide (40 ml.) and hydrogen peroxide (16 ml.; 100-vol.). The diacyl peroxide, which separated as a white powder, was collected and dried. The filtrate contained some unchanged acid chloride which, on addition of sodium hydroxide (5 g.) followed by vigorous shaking, was converted into more peroxide. The total product crystallised from methanol in colourless plates, m. p. 80° (13·6 g.), and was shown by analysis (acidified potassium iodide/thiosulphate titration) to be *m-tert.*-butylbenzoyl peroxide (98·1% pure).

3-tert.-*Butyldiphenyl.*—A solution of the peroxide (9·9 g.) in benzene (400 ml.; "AnalaR," dried over sodium) was boiled under reflux for 3 days. The volume of the pale yellow solution was reduced, and the residual oil was boiled under reflux with 2N-sodium hydroxide (200 ml.) for 8 hr. The organic layer was extracted with benzene (4 times), and the combined extracts were washed with water (twice) and dried ($CaCl_2$). The solvent was removed and the residue was distilled and redistilled *in vacuo*, to give a colourless oil (3·8 g.), b. p. 105°/0·4 mm., n_D^{20} 1·5680 (Found: C, 91·2; H, 8·8. $C_{16}H_{18}$ requires C, 91·4; H, 8·6%).

Decomposition of o-tert.-*Butyl-*N-*nitrosoacetanilide in Benzene.*—*o-tert.*-Butylnitrobenzene (70 g.) was reduced in boiling ethanol solution by iron dust (70 g.) and hydrochloric acid (8 ml.; *d* 1·16) to *o-tert.*-butylaniline (b. p. 64°/0·1 mm.; 80%). Its acetyl derivative, m. p. 163° (from benzene–light petroleum), was converted into *o-tert.*-butyl-*N*-nitrosoacetanilide [m. p. 62° (decomp.); 90%] by the method described above for the *p*-isomeride. The nitroso-compound (8 g.) was allowed to decompose in benzene under conditions similar to those employed for the decomposition of the *p*-isomeride. Removal of the solvent and distillation of the residue gave a yellow oil (1·6 g.), b. p. 52—65°/0·1 mm., and *o-tert.*-butylacetanilide as a yellow solid (0·6 g.), b. p. 70°/0·1 mm., m. p. and mixed m. p. 160°. The yellow oil was dissolved in benzene (20 ml.)

and washed with sulphuric acid as in the case of the *p*-isomeride. Evaporation of the solvent afforded diphenyl in colourless plates, m. p. and mixed m. p. 68°. The decomposition was repeated with the nitroso-compound (35 g.) in benzene (400 ml.), giving *o-tert.*-butylacetanilide (3 g.) and a pale yellow liquid (15 g.), b. p. 100—128°/16 mm., n_D^{20} 1·5120. Careful fractionation of the latter gave *tert.*-butylbenzene (2·93 g.), b. p. 61—62°/15 mm., n_D^{20} 1·4930, proved by conversion into the *p*-sulphonamido-derivative, m. p. and mixed m. p. 137·5°, and a liquid (A) (10 g.), b. p. 115—125°/15 mm., n_D^{20} 1·5170 (Found: C, 78·4; H, 8·0%), which contained oxygen and could not be further fractionated. A portion (2 g.) was boiled under reflux with 3N-sodium hydroxide (100 ml.) for 5 hr. The organic layer was extracted with benzene, and evaporation of the solvent gave diphenyl, m. p. and mixed m. p. 68—69°. The basic portion was acidified and extracted with benzene (four times) and washed with water (twice), and the solvent was removed. The residual oil, which was not solid at 0°, was phenolic and was converted into the corresponding aryloxyacetic acid. The crude acid (m. p. 100—109°) was recrystallised to constant m. p. (114°) from benzene–light petroleum (Found: C, 68·8; H, 7·3. Calc. for $C_{12}H_{16}O_3$: C, 69·2; H, 7·7%). The analysis corresponds to that of a *tert.*-butylphenoxyacetic acid. The *o*- and *p*-isomerides have been previously described and have m. p.s 145—146° and 86° respectively. It appears likely that the phenolic product of the hydrolysis was a mixture of isomeric *tert.*-butylphenols, the *m*-isomeride preponderating. These phenols were formed as the result of hydrolysis of esters formed during the original decomposition. Although no acetic acid was isolated it is considered that the esters were the *tert.*-butylphenyl acetates, and a mixture consisting of 15% of diphenyl and 85% of *tert.*-butylphenyl acetate has the same percentage composition as that found for liquid (A).

2-tert.-*Butyldiphenyl.*—*o-tert.*-Butylbenzoic acid, prepared by Crawford and Stewart's method (*loc. cit.*), was converted into the acid chloride by the action of thionyl chloride. *o-tert.*-Butylbenzoyl peroxide was not formed under the conditions employed for the formation of the *m*-isomeride but the following modification was successful: Powdered sodium peroxide (2 g.) was added carefully to water (4 ml.) stirred vigorously in a cooling-bath. The acid chloride (5 g.) was added during 1 hr., followed by sodium peroxide (1·5 g.), and the stirring was continued for 2 hr. The yellow oil which separated was extracted with light petroleum and the combined extracts were washed with 2N-sodium hydroxide (twice), then water (once), and dried ($CaCl_2$). The solvent was removed by evaporation at room temperature and the residual oil was triturated with methanol until it solidified. The pale yellow solid (0·9 g.; m. p. 47—51°) was recrystallised with difficulty from methanol. It had m. p. 59° and liberated iodine from acid potassium iodide solution. The peroxide (0·3 g.) was decomposed in benzene (100 ml.; "AnalaR," sodium-dried) by boiling under reflux for 72 hr. Most of the benzene (90 ml.) was removed by distillation through a 12" helix-packed column, which was afterwards washed with ether (15 ml.), the washings being combined with the residue. The ether was removed from the distillation flask by evaporation at room temperature and the yellow residue was boiled under reflux with 2N-sodium hydroxide (50 ml.) for 4 hr. The remainder of the working-up procedure was identical with that used in the preparation of 3-*tert.*-butyldiphenyl described above. The product (90 mg.) was a low-melting solid which contained oxygen, probably resulting from the presence of ester. The entire product was dissolved in light petroleum (b. p. 40—60°; 10 ml.) and chromatographed on an alumina column (6" × ¼"). Elution with light petroleum (b. p. 40—60°) gave 2-tert.-*butyldiphenyl* as a colourless crystalline solid (60 mg.), m. p. 31—34° (Found: C, 91·8; H, 8·0. $C_{16}H_{18}$ requires C, 91·4; H, 8·6%). Its infra-red spectrum was recorded and it had bands at 735, 755, and 779 cm.$^{-1}$, which are characteristic of a 2-substituted diphenyl, and at 1200 and 901 cm.$^{-1}$, which are characteristic of a *tert.*-butyl group.

2 : 5-*Di*-tert.-*butyldiphenyl.*—The combined diaryl fractions from experiments 4, 5, 6, and 7, after portions had been analysed for nitrodiphenyl content, were reduced in ethanol (60 ml.) by granulated tin and hydrochloric acid. Unchanged tin was removed by filtration and some ethanol (25 ml.) removed from the filtrate by evaporation. At this point a colourless oil separated which solidified on cooling. The crystals (0·5 g.) were removed from the surface of the mixture by hand, and recrystallisation from methanol gave 2 : 5-*di*-tert.-*butyldiphenyl* in colourless needles, m. p. 94·2° (Found: C, 90·2; H, 9·8. $C_{20}H_{26}$ requires C, 90·2; H, 9·8%). The infra-red spectrum of this compound as a crystalline powder in a Nujol mull was recorded. It had bands at 1200, 822·5, 761·5 cm.$^{-1}$, indicative of a 2 : 5-disubstituted diphenyl containing at least one *tert.*-butyl group.

Note: The preparation of 3-iododiphenyl as a colourless oil (b. p. 114·5°/0·3 mm.) was reported in Part IV (*loc. cit.*). This has now solidified (m. p. 26·5°) and its m. p. is unchanged on recrystallisation from light petroleum (b. p. 40—60°).

DISCUSSION.

Partial Rate Factors for Phenylation.—(i) tert.-*Butylbenzene.* The relative rate of substitution in *tert.*-butylbenzene ${}^{\mathrm{PhBu^t}}_{\mathrm{PhH}}K$ may be calculated from ${}^{\mathrm{PhBu^t}}_{\mathrm{PhNO_2}}K$ and ${}^{\mathrm{PhNO_2}}_{\mathrm{PhH}}K$, the determination of which was reported in Part II (*loc. cit.*). In this way ${}^{\mathrm{PhBu^t}}_{\mathrm{PhH}}K$ is found to be 0·87. By using this value and the mean values obtained in the spectrographic analysis for the ratio of isomerides (Table 4), the following values are obtained for the partial rate factors :

$$F_o = 0{\cdot}63 \quad F_m = 1{\cdot}28 \quad F_p = 1{\cdot}41$$

Thus, the *o*-position is deactivated, while the *m*- and the *p*-positions are activated slightly, the overall effect being deactivation. This is the first example of deactivation in homolytic phenylation of aromatic nuclei encountered by us. The simplest interpretation is that the large *tert.*-butyl group exerts a selective steric repression of *o*-substitution, and since substitution by phenyl radicals takes place mainly at the *o*-position (Parts I—V, *loc. cit*; Hey, Pengilly, and Williams, unpublished results) in all cases so far studied, this repression results in a slight overall deactivation of the molecule. A similar steric inhibition of *o*-substitution has been observed in the heterolytic nitration of *tert.*-butylbenzene (Brown and Nelson, *loc. cit.*; Cohn, Hughes, Jones, and Peeling, *Nature*, 1952, **169**, 29). It should be noted that the *amounts* of the isomerides formed in the phenylation reaction vary in the order $m > p > o$, while in the nitration reaction the order is $p > o > m$, which is a further indication that the electronic requirements for homolytic and heterolytic aromatic substitution reactions are different. The formation of a large amount of polyphenylated *tert.*-butylbenzene during the phenylation of *tert.*-butylbenzene is consistent with the low value determined for ${}^{\mathrm{PhBu^t}}_{\mathrm{PhH}}K$, because the *tert.*-butyldiphenyls first produced by monophenylation are much more reactive than the substrate molecule (Cadogan, Hey, and Williams, Part V). It appears that the decomposition of benzoyl peroxide in dilute solutions in " fast " solvents, such as nitrobenzene, 1 : 3 : 5-trichlorobenzene, and diphenyl, produces negligible amounts of polyphenylation products, whereas decomposition in less reactive solvents, such as the monohalogenobenzenes, benzene, and *tert.*-butylbenzene, affords an appreciable amount of polyphenylation. Decomposition of benzoyl peroxide in a mixture of a " fast " and a " slow " solvent, as in the determination of ${}^{\mathrm{PhBu^t}}_{\mathrm{PhNO_2}}K$, results in a negligible amount of residue.

(ii) p-*Di*-tert.-*butylbenzene.* The rate of phenylation relative to benzene of *p*-di-*tert.*-butylbenzene is obtained from the value of ${}^{p\text{-}\mathrm{But_2C_6H_4}}_{\mathrm{PhNO_2}}K$ by multiplication by 4, since ${}^{\mathrm{PhNO_2}}_{\mathrm{PhH}}K$ is equal to 4 (Part II). Thus, ${}^{p\text{-}\mathrm{But_2C_6H_4}}_{\mathrm{PhH}}K = 0{\cdot}63$. It follows that the partial rate factor for phenylation in any position in *p*-di-*tert.*-butylbenzene is 0·93. The introduction of a *tert.*-butyl group into the *p*-position of *tert.*-butylbenzene therefore produces further deactivation of the molecule but increases the partial rate factor of the *o*-position. A decrease in overall activation is to be expected because the number of positions available for substitution has been decreased, and each of the four positions is now *ortho* with respect to a *tert.*-butyl group. The increase in the value of the partial rate factor at the *o*-position, on the other hand, indicates that the intrinsic effect of the *tert.*-butyl group is possibly one of slight activation, as observed for all other groups so far investigated, although the fact that all four positions are also *meta*- to a *tert.*-butyl group, and are therefore slightly activated, may be a contributory factor.

The results of these experiments, together with those previously reported, show that, whereas homolytic substitution reactions are very much less sensitive to polar influences than are heterolytic reactions, they are nevertheless susceptible in the normal manner to steric effects.

Decomposition of o-tert.-*Butyl*-N-*nitrosoacetanilide in Benzene.*—This decomposition took an anomalous course, the expected product, 2-*tert.*-butyldiphenyl, not being isolated. The main products were *tert.*-butylbenzene, *o-tert.*-butylacetanilide, diphenyl, and the isomeric *tert.*-butylphenyl acetates. The results of this non-quantitative experiment suggest that the formation of *tert.*-butylbenzene is due to the preferred abstraction by an *o-tert.*-butylphenyl radical of a hydrogen atom from the solvent, and the phenyl radical so

formed then attacks the solvent to give diphenyl. The quantities of diphenyl and *tert.*-butylbenzene formed are approximately equivalent. Examples of the abstraction of an " aromatic " hydrogen atom in place of the normal nuclear arylation have been reported by Haworth and Hey (*J.*, 1940, 364). The formation of the isomeric *tert.*-butylphenyl acetates is considered unlikely to be due to attack of free acetoxy-radicals on *tert.*-butylbenzene, because benzene was present in large excess and no phenyl acetate was detected. The process is probably intermolecular. *o-tert.*-Butylacetanilide results from denitrosation, a similar example with 2-acetamido-*N*-nitrosodiphenyl having been reported in Part V. The absence of 2-*tert.*-butyldiphenyl must be attributed to the existence of a large energy barrier, possibly due to steric effects, with the result that all the processes mentioned above become energetically favoured.

Thanks are accorded to the Department of Scientific and Industrial Research for the award of a Maintenance Grant (to J. I. G. C.) during the tenure of which part of this work was carried out, to the Delegacy of King's College, London, for the award of a Tutorial Studentship (to J. I. G. C.), and to Dr. W. C. Price for providing facilities for the infra-red measurements.

KING'S COLLEGE (UNIVERSITY OF LONDON),
STRAND, LONDON, W.C.2. [*Received, May 4th,* 1954.]

Reactions of α-Halogeno-ketones with Aromatic Compounds. Part I. Reactions of Chloroacetone and 3-Chlorobutanone with Phenol and its Ethers.

By S. HUSAIN ZAHEER, BALDEV SINGH, BHARAT BHUSHAN, P. M. BHARGAVA, I. K. KACKER, K. RAMACHANDRAN, V. D. N. SASTRI, and N. SHANMUKHA RAO.

[Reprint Order No. 5378.]

Condensation of α-halogeno-ketones, R·CHCl·COR′ (R = H or Me; R′ = Me), with phenol or its ethers in the presence of concentrated sulphuric acid or aluminium chloride yielded substituted stilbene derivatives.

CONDENSATION of chloroacetone with phenol and its ethers in presence of concentrated sulphuric acid and anhydrous aluminium chloride as catalysts has been studied with a view to prepare compounds, $CH_2Cl{\cdot}CMeAr_2$, which might have insecticidal properties like those of DDT. Lippmann has reported (*Ber.*, 1912, **45**, 2490) that chloroacetone and phenol in the presence of hydrochloric acid at 100° give 1 : 2 : 2-tris-*p*-hydroxyphenylpropane. In our experiments, phenol reacted with chloroacetone in the presence of concentrated sulphuric acid at −10° to −5°, giving good yields of *trans*-4 : 4′-dihydroxy-α-methylstilbene, but at higher temperatures the reaction tended to be very vigorous, yielding dark sulphur-containing products. The diphenol and its diacetate and dimethyl ether were identical with the compounds synthesised earlier by Dodds *et al.* (*Proc. Roy. Soc.*, 1944, *B*, **132**, 83). Anisole and phenetole reacted similarly with chloroacetone, yielding 4 : 4′-dimethoxy- and 4 : 4′-diethoxy-α-methylstilbenes, which were also prepared by alkylation of the diphenol. The same three products were also obtained, although in lower yields, when chloroacetone was condensed with phenol, anisole, or phenetole in the presence of aluminium chloride at ~0°, with or without light petroleum as diluent.

When 3-chlorobutanone was used in place of chloroacetone, similar condensations occurred with phenol and anisole at 0°, yielding 2 : 3-di-*p*-hydroxyphenylbut-2-ene (characterised as its diacetyl derivative) and its dimethyl ether respectively, also obtained by Dodds *et al.* (*loc. cit.*).

In a preliminary note Bhargava and Zaheer (*Nature*, 1953, **171**, 746) postulated a reaction mechanism involving a Friedel–Crafts type of reaction as the first step. Sastri, Shanmukha Rao, and Zaheer (*Current Sci.*, 1953, **22**, 338), however, suggested a more probable reaction sequence, in which first the carbonyl group of the ketone reacts at the

p-position of the aromatic compound, a subsequent rearrangement involving migration of one of the aromatic nuclei to the adjacent carbon atom and dehydrohalogenation.

Similar condensations with 2-chloropentan-3-one and 4-chlorohexan-3-one are being attempted with a view to synthesis of œstrogenic compounds.

Experimental

Phenol, anisole, and phenetole were freshly distilled before use. Chloroacetone (B.D.H.) was used as such. 3-Chlorobutanone was prepared by the chlorination of butanone (Korschun, *Ber.*, 1905, **38**, 1128).

4 : 4′-*Dihydroxy-α-methylstilbene.*—(*a*) Concentrated sulphuric acid (29·4 g., 0·3 mole) was added dropwise during 1 hr. to a mechanically stirred mixture of phenol (56·4 g., 0·6 mole) and chloroacetone (27·75 g., 0·3 mole) cooled to about −10°, the stirring being continued for a further 2—3 hr. The orange-red pasty mass was treated with ice-cold water, a pale orange semi-solid product separating. This was washed with cold water and crystallised from hot aqueous alcohol. Pale orange crystals together with a small quantity of a colourless oil were obtained. The crystals which were collected and washed with a little light petroleum, had m. p. 115—120° (45 g.). Two recrystallisations from alcohol raised the m. p. to 176—179°; a further recrystallisation from benzene gave white shining plates, m. p. 182—183° (66·4%).

(*b*) A mixture of chloroacetone (4·6 g., 0·05 mole) and phenol (9·4 g., 0·1 mole) was added dropwise in 30—45 min. to a well-stirred suspension of anhydrous aluminium chloride (6·67 g., 0·05 mole) in light petroleum (b. p. 40—60°), cooled in an ice-bath. An orange-red sticky mass began to separate immediately, but stirring was continued for another 2 hr. Cold dilute hydrochloric acid was then added slowly and the upper fluorescent petroleum layer was separated, washed with water, dilute sodium hydrogen carbonate solution, and again with water, dried (Na_2SO_4), and evaporated. The sticky residue, twice crystallised from 25—30% alcohol, melted at 182—183° (3 g., 26·6%). The mother-liquor on concentration yielded a purple oil, which deposited some crystals during a long period.

The *diacetate*, prepared by acetyl chloride in pyridine at 0° and recrystallised from alcohol, formed plates, m. p. 123—124° (2·2 g. from 2·0 g.) (Found : C, 73·2; H, 6·1. $C_{19}H_{18}O_4$ requires C, 73·55; H, 5·8%). On hydrolysis with 15% aqueous potassium hydroxide, the diphenol was obtained in theoretical yield. The *dipropionate*, similarly prepared and crystallised, formed needles, m. p. 107—108° (2 g. from 2·4 g.) (Found : C, 75·0; H, 6·8. $C_{21}H_{22}O_4$ requires C, 74·6; H, 6·5%).

The diphenol (2·13 g.), methyl iodide (8·52 g.), anhydrous potassium carbonate (2·76 g.), and acetone (3·48 g.) were refluxed for 3—4 hr. After removal of acetone and excess of methyl iodide and treatment with water, a solid *dimethyl ether* was obtained, as plates (from alcohol), m. p. 124° (2·2 g.) (Found : C, 79·7; H, 7·3. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%); the *diethyl ether*, similarly prepared, formed needles, m. p. 105—106° (Found : C, 80·3; H, 8·0. $C_{19}H_{22}O_2$ requires C, 80·85; H, 7·8%), and the *di*-n-*propyl ether* formed plates, m. p. 107—108° (Found : C, 81·1; H, 8·8. $C_{21}H_{26}O_2$ requires C, 81·3; H, 8·4%), and the *diallyl ether*, similarly prepared but crystallised from acetone, formed plates, m. p. 94—95°, sparingly soluble in alcohol, benzene, and ethyl acetate (Found : C, 81·5; H, 7·5. $C_{21}H_{22}O_2$ requires C, 82·35; H, 7·2%).

4 : 4′-*Dimethoxy-α-methylstilbene.*—(*a*) Concentrated sulphuric acid (9·8 g., 0·1 mole) was added dropwise during 0·5 hr. to a stirred mixture of anisole (16·2 g., 0·15 mole) and chloroacetone (6·9 g., 0·075 mole) at 0°, and the mixture was stirred for a further 4—5 hr. Water was then added, and the liquid which separated was extracted with ether. The extract was washed twice with water and dried ($CaCl_2$), and the ether removed. The resulting red viscous liquid was refluxed in hot alcohol for a few hours. Part of the alcohol was then distilled off and on cooling 4 : 4′-dimethoxy-α-methylstilbene crystallised (15 g., 77·5%). Recrystallised from hot alcohol it had m. p. and mixed m. p. with the above dimethyl ether, 124°.

(*b*) Reaction of chloroacetone (4·6 g., 0·05 mole) and anisole (10·8 g., 0·1 mole) in the presence of anhydrous aluminium chloride, as for the diphenol, yielded the dimethyl ether, m. p. and mixed m. p. 124°. The mother-liquor on prolonged refluxing and cooling yielded more of this compound (total yield 27·9%).

4 : 4′-Diethoxy-α-methylstilbene was similarly prepared from phenetole, chloroacetone, and sulphuric acid (yield, 59·4%); it had m. p. and mixed m. p. 105—106°. Use of aluminium chloride as catalyst gave a 18·5% yield.

2 : 3-*Di*-p-*hydroxyphenylbut*-2-*ene.*—(*a*) Concentrated sulphuric acid (14·7 g., 0·15 mole) was added dropwise in 30 min. to a stirred mixture of phenol (9·4 g., 0·1 mole) and 3-chlorobutan-2-one

(5·3 g., 0·05 mole), stirring being continued for 2—3 hr. Treatment with ice-water and washing by decantation gave a dark red viscous mass, which was taken up in ether. The fluorescent ether layer was dried and the ether removed. The residual viscous liquid (10·2 g.) was steam-distilled to remove traces of phenol and taken up in ether, dried, and, after removal of ether, acetylated with acetic anhydride and sodium acetate. The oil obtained on addition of water was taken up in ether and after removal of ether, distilled under reduced pressure. The fraction coming over at 200—210°/2 mm. partly solidified. The crystals were filtered off, washed with cold ether–light petroleum, and twice recrystallised from alcohol. Colourless needles of 2 : 3-di-*p*-acetoxyphenylbut-2-ene (1·3 g., 8·0%), m. p. 123—124°, were obtained (Found : C, 74·3; H, 6·3. Calc. for $C_{20}H_{20}O_4$: C, 74·1; H, 6·2%). A mixed m. p. with an authentic specimen showed no depression.

The free diphenol was isolated only as an oil. When the reaction time was increased to 6—7 hr., and even when the quantity of sulphuric acid was reduced to one mol., only a semi-solid mass was obtained which, although it solidified when heated with ligroin (b. p. 80—100°), did not have a sharp m. p. and could not be purified.

(*b*) Anhydrous aluminium chloride (6·67 g., 0·05 mole) was added in small lots during 30 min. to a well-stirred, ice-cooled solution of phenol (9·4 g., 0·1 mole) and 3-chlorobutan-2-one (5·32 g., 0·05 mole) in dry light petroleum (100 ml.; b. p. 40—60°). A pink product, gradually deepening in colour to red, slowly separated. After another 3 hours' stirring, ice water (200 ml.) and a little dilute hydrochloric acid were added, followed by ether, which dissolved the reaction mass. The solvent layer was separated, washed successively with water, sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated. The residue was steam-distilled and from the non-volatile portion, after washing with ether–light petroleum, a small quantity of solid melting at 194—196° was obtained, presumably the diphenol. The non-volatile residue on acetylation yielded the diacetate, m. p. and mixed m. p. with the earlier sample, 123—124°.

With acetic anhydride in pyridine it gave a diacetate, m. p. 124° (from alcohol) alone or mixed with an authentic specimen.

2 : 3-*Di*-p-*methoxyphenylbut*-2-*ene*.—(*a*) Concentrated sulphuric acid (14·7 g., 0·15 mole) was added in 1 hr. to a stirred mixture of anisole (10·8 g., 0·1 mole) and 3-chlorobutanone (5·3 g., 0·05 mole) cooled in ice. After a further 4 hours' stirring, the dark-red semi-solid mass was treated with crushed ice and extracted with ether. The extract was washed with dilute sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated. On distillation, a little unchanged anisole (0·5 g.) came over first, followed by the main fraction, b. p. 190—200°/2 mm. This solidified on cooling in ice. Two crystallisations from light petroleum gave colourless needles, m. p. 129—130° (8 g., 59%) (Found : C, 80·0; H, 7·7; OMe, 22·4. Calc. for $C_{18}H_{20}O_2$: C, 80·6; H, 7·5; 2OMe, 23·2%). A mixed m. p. with an authentic sample prepared according to the procedure of Sisido, Nozaki, and Kurihara (*J. Amer. Chem. Soc.*, 1949, **71**, 2037) showed no depression.

Some experiments, yielded also an ether-insoluble substance which dissolved in benzene and was precipitated therefrom by light petroleum. This amorphous white powder, m. p. 180—190°, contained sulphur and was not investigated further. Reaction at 25—30° gave a dark viscous mass from which no solid could be isolated.

(*b*) A cooled mixture of anisole (10·8 g., 0·10 mole) and 3-chlorobutan-2-one (5·3 g., 0·05 mole) was added dropwise in 1 hr. with stirring to anhydrous aluminium chloride (13·35 g., 0·1 mole) cooled in ice–salt. After 5 hours' stirring, the dark-red solid mass was decomposed with crushed ice and dilute hydrochloric acid and extracted with ether. The extract was washed with dilute hydrochloric acid, followed by dilute sodium hydrogen carbonate solution and distilled water, and dried (Na_2SO_4). The solvent was distilled off and the residue distilled under reduced pressure. Unchanged anisole (0·5 g.) distilled first and then 5·5 g. of a product of b. p. 180—200°/2 mm., which solidified partly and yielded 2 g. of colourless needles. After two crystallisations from light petroleum, it had m. p. and mixed m. p. with the previous sample, 130—131° (yield 41%).

Demethylation. To the Grignard reagent from 2 g. of magnesium and 12 g. of methyl iodide was added a solution of 2 g. of the last compound in 30 ml. of ether. The solvent was removed and the residue heated at about 170° for 40 min. On working up in the usual way, colourless prisms of 2 : 3-di-*p*-hydroxyphenylbut-2-ene, m. p. 194—195°, were obtained.

CENTRAL LABORATORIES FOR SCIENTIFIC AND INDUSTRIAL RESEARCH,
HYDERABAD-DECCAN, 7, INDIA. [*Received, May 11th*, 1954.]

The Decarboxylative Acylation of Succinic Acid Derivatives. Part I. Benzamidosuccinic Acid.

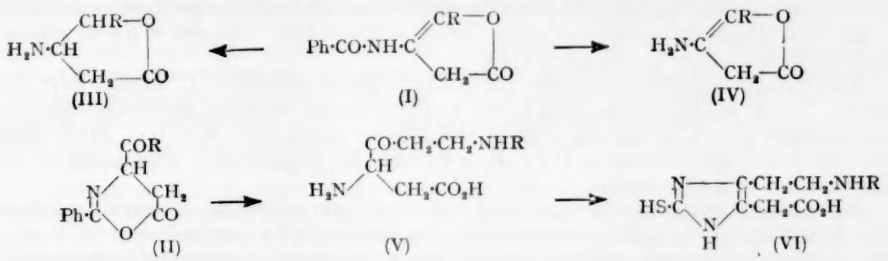
By Alexander Lawson.

[Reprint Order No. 5398.]

Benzoylaspartic anhydride has been submitted to decarboxylative acylation (Lawson, *J.*, 1953, 1046) by several acid anhydrides, lactones of type (I) or (II) or mixtures thereof being obtained. With aromatic acid anhydrides and nicotinic anhydride type (I) predominated, and with benzoic and *p*-acetoxybenzoic anhydrides these have been used to produce amines chemically related to sympathomimetic drugs. With β-benzamidopropionic anhydride the product was of type (II) and it was converted into the corresponding 2-mercaptohistamine derivative by hydrolysis and treatment with thiocyanate.

The reaction between benzoylaspartic anhydride and simple aliphatic acid anhydrides which gave rise to benzamido-lactones (I; R = alkyl) and ketones (II; R = alkyl) (Lawson, *J.*, 1953, 1046) has been extended to other acid anhydrides with a view to the preparation of amines of pharmacological interest. The reactions were carried out with excess of the anhydride in boiling xylene or toluene until the carbon dioxide evolution ceased. The speed of reaction varied considerably from case to case.

With benzoic anhydride, the main product was the lactone (I; R = Ph), although some ketone (II; R = Ph) was also formed, as proved by the isolation of the corresponding mercaptoglyoxaline after hydrolysis of the gum left after evaporation of the mother-liquor from (I) and treatment with thiocyanate. As with the corresponding aliphatic derivatives, hydrolysis of the lactone (I) removed the amido-group as benzoic acid and ammonium chloride, with formation of a ketone. It was, however, possible to hydrogenate the lactone by using a relatively large quantity of Raney nickel, and hydrolysis of the saturated lactone gave the amine (III; R = Ph). This substance, having a structure related to that of norephedrine, is being tested pharmacologically.



In the reaction between acetylsalicylic anhydride and benzoylaspartic anhydride carbon dioxide was evolved much more slowly. The products (I; R = Me) and (II; R = Me) corresponded to those obtained by the direct action of acetic anhydride on benzoylaspartic anhydride (Lawson, *loc. cit.*), which is not surprising when one considers the ease with which acetylsalicylic acid liberates acetic anhydride on heating.

With *p*-anisic anhydride the reaction was again relatively slow, and the small yield of the lactone (I; R = *p*-C_6H_4·OMe) precluded further work with it.

p-Acetoxybenzoic anhydride also reacted slowly with benzoylaspartic anhydride but, with a longer reaction time, yields of over 50% of the lactone (I; R = *p*-C_6H_4·OAc) were obtained. Dissolution of the product in dilute aqueous sodium hydroxide liberated the free phenol. Hydrogenation of the double bond in this substance could not be effected under the conditions used with the benzoic anhydride product; this difficulty was not surprising in view of the quaternary nature of the carbon atoms at the double bond, but

the difference between the phenyl and the *p*-hydroxyphenyl derivatives is not readily understandable. At 40 atmospheres in the presence of platinum black, however, the free phenol was hydrogenated and analysis of a phenolic compound isolated in small yield indicated an uptake of six hydrogen atoms. This substance liberated its nitrogen as ammonia, and gave *cyclo*hexanecarboxylic acid on hydrolysis. It was, therefore, 3-hexahydrobenzamido-4-hydroxy-4-*p*-hydroxyphenylbut-3-enoic lactone.

Like benzamide the unsaturated lactone (I; R = *p*-C_6H_4·OAc) reacted with sodium amalgam to produce benzaldehyde, and as a result it was possible to remove the benzoyl group leaving the unsaturated amino-lactone (IV; R = *p*-C_6H_4·OH). This substance, being an αβ-unsaturated amine, was only feebly basic; it was an analogue of β-amino-α-angelicalactone (Dakin and West, *J. Biol. Chem.*, 1928, **78**, 750). On acetylation it gave an acetyl derivative, judged to contain *N*-acetyl since it showed phenolic properties.

In the reaction between *m*-acetoxybenzoic anhydride and benzoylaspartic anhydride the main product was the unsaturated lactone (I; R = *m*-C_6H_4·OAc), though in this case a small quantity of the ketone (II; R = *m*-C_6H_4·OAc) was also isolated and converted in the usual manner into the mercaptoglyoxaline. Mild hydrolytic treatment and hydrogenation of the unsaturated lactone produced substances analogous to those obtained in the *p*-series.

Phenylacetic anhydride reacted readily under the usual conditions with benzoylaspartic anhydride to give the unsaturated lactone (I; R = CH_2Ph). The phenylhydrazone of a ketone $C_{18}H_{15}O_3N$ was obtained from the reaction mixture indicating the simultaneous formation of the ketone (II; R = CH_2Ph).

From the reaction between nicotinic anhydride and benzoylaspartic anhydride a basic substance $C_{16}H_{12}O_3N_2$ and an amphoteric compound $C_{16}H_{14}O_4N_2$ were isolated. Apart from salt formation both substances were unaffected by boiling dilute hydrochloric acid or warm acetic anhydride, showing that a relation of substance to its anhydride probably did not apply. With concentrated hydrochloric acid both substances gave ammonium chloride, benzoic acid, and an unidentified ketone. The base $C_{16}H_{12}O_3N_2$, being analogous in formula to other products of the decarboxylative acylation of aspartic anhydride and giving similar reactions, is assigned the structure (I; R = C_5H_4N). No compound analogous to $C_{16}H_{14}O_4N_2$ was isolated from the other acylations described. This substance gave a phenylhydrazone and an oxime, and was the only ketonic condensation product encountered in this work which did not give an amino-ketone on hydrolysis. Neither of the substances could be hydrogenated at one atmosphere.

β-Benzamidopropionic anhydride and benzoylaspartic anhydride in toluene gave the ketone (II; R = CH_2·CH_2Bz), which was hydrolysed first to either the monobenzoyldiamino-ketone (V; R = Bz) and then to the diamino-ketone (V; R = H). From these two the 2-mercaptohistamines (VI; R = Bz and H, respectively) were prepared by condensation with thiocyanate.

β-Phthalimidopropionic anhydride and benzoylaspartic anhydride also gave the ketone (II; R = CH_2·CH_2·$C_8H_4O_2N$), which readily lost the benzoyl group on hydrolysis to give on subsequent treatment with thiocyanate 2-mercapto-4-phthalimidoethyl-5-glyoxalinylacetic acid. Removal of the phthalimido-group was not effected by prolonged boiling with hydrochloric acid.

Experimental

Acetoxybenzoic anhydrides and *p*-anisic anhydride were prepared in good yield by using thionyl chloride in benzene in the presence of pyridine (D.R.-P. 201,325/1907). m-*Acetoxybenzoic anhydride*, needles (from ethyl acetate), had m. p. 103° (Found: C, 63·0; H, 4·2. $C_{18}H_{14}O_7$ requires C, 63·2; H, 4·1%).

Action of Benzoic Anhydride on Benzoylaspartic Anhydride.—Benzoylaspartic anhydride (2 g.) was heated with benzoic anhydride (6 g.) in boiling xylene (30 ml.) till carbon dioxide evolution ceased (about 1 hr.). Next morning the crystalline product (2 g.) was collected. Recrystallisation from ethyl acetate gave colourless prisms of *3-benzamido-4-phenylbut-3-enoic lactone*, m. p. 152° (Found: C, 72·5; H, 4·6; N, 5·15. $C_{17}H_{13}O_3N$ requires C, 73·2; H, 4·7; N, 5·05%). Evaporation of the xylene filtrate under reduced pressure, followed by hydrolysis with concentrated hydrochloric acid at 155° and removal of the benzoic acid by filtration and

hydrochloric acid by distillation, left a small residue which on treatment with potassium thiocyanate gave **2-*mercapto*-4-*phenyl*-5-*glyoxalinylacetic acid*** which, recrystallised from aqueous ethanol, had m. p. 244° (decomp.) (Found: C, 56·2; H, 4·5. $C_{11}H_{10}O_2N_2S$ requires C, 56·4; H, 4·3%).

The phenylbutenoic lactone (1 g.) was hydrogenated in ethyl acetate solution (100 ml.) with Raney nickel (5 g.). The theoretical volume of hydrogen was taken up in 2 hr. Removal of the solvent left **3-*benzamido*-4-*hydroxy*-4-*phenylbutanoic lactone***, colourless felted needles, m. p. 182°, in theoretical yield (Found: C, 72·0; H, 5·35. $C_{17}H_{18}O_3N$ requires C, 72·6; H, 5·3%). The lactone (1 g.) was hydrolysed with boiling 20% aqueous hydrochloric acid for 1 hr. and the benzoic acid removed by filtering the cooled solution. Evaporation of the filtrate left **3-*amino*-4-*hydroxy*-4-*phenylbutanoic lactone hydrochloride*** (0·4 g.), needles, m. p. 234° (decomp.) (from 90% aqueous ethanol) (Found: C, 55·5; H, 5·7; N, 6·4. $C_{10}H_{12}O_2NCl$ requires C, 56·2; H, 5·6; N, 6·6%). The free base precipitated from an aqueous solution of the hydrochloride by sodium hydrogen carbonate was a wax which decomposed when kept.

Reaction with Acetylsalicylic Anhydride.—Benzoylaspartic anhydride (1 g.) and acetylsalicylic anhydride (2·5 g.) were heated in boiling xylene (20 ml.). After 5 hr. the xylene was evaporated under reduced pressure and the residue dissolved in hot benzene which was extracted with aqueous sodium hydrogen carbonate. The benzene solution after concentration gave 3-benzamido-4-hydroxypent-3-enoic lactone, m. p. 174°. The mother-liquor, on treatment with dinitrophenylhydrazine in ethanol, gave ethyl β-benzamido-γ-oxovalerate 2 : 4-dinitrophenylhydrazone, and on hydrolysis of the residue left after evaporation of the benzene, followed by treatment with potassium thiocyanate, a small amount of 2-mercapto-4-methyl-5-glyoxalinylacetic acid was obtained.

Reaction with p-*Anisic Anhydride.*—*p*-Anisic anhydride (2 g.) was heated in boiling xylene (20 ml.) with benzoylaspartic anhydride (1 g.) for several hours. After cooling and addition of benzene the solution was extracted with aqueous sodium hydrogen carbonate and then with N-sodium hydroxide. The second extract was treated with solid carbon dioxide till there was no further precipitation. The **3-*benzamido*-4-*hydroxy*-4-p-*methoxyphenylbut*-3-*enoic lactone*** so obtained and recrystallised from ethanol (prisms) had m. p. 132° (Found: C, 70·0; H, 4·9; N, 4·8. $C_{18}H_{15}O_4N$ requires C, 70·0; H, 4·9; N, 4·5%).

Reaction with p-*Acetoxybenzoic Anhydride.*—Benzoylaspartic anhydride (1 g.) was mixed with *p*-acetoxybenzoic anhydride (2·6 g.) and the suspension in dry xylene (20 ml.) was boiled until evolution of carbon dioxide ceased (about 6 hr.). The solution was then kept overnight at 0°, and the product (1·2 g.) was collected. After trituration with anhydrous ether, **4-p-*acetoxyphenyl*-3-*benzamido*-4-*hydroxybut*-3-*enoic lactone*** recrystallised from aqueous ethanol in colourless rosettes, m. p. 167° (Found: C, 67·4; H, 4·5; N, 4·1. $C_{19}H_{15}O_5N$ requires C, 67·6; H, 4·5; N, 4·2%). From this substance the phenol was obtained by hydrolysis, by boiling dilute hydrochloric acid for a short time or by dissolution in a small quantity of 3N-sodium hydroxide and precipitation with acid. When sodium hydroxide was used the yield of **3-*benzamido*-4-p-*hydroxyphenyl*-4-*hydroxybut*-3-*enoic lactone*** was quantitative. It recrystallised from aqueous ethanol in needles, m. p. 212° (Found: C, 69·3; H, 4·4; N, 4·4. $C_{17}H_{13}O_4N$ requires C, 69·1; H, 4·4; N, 4·7%).

Attempts made to hydrogenate the acetyl derivative or the phenol under the conditions recorded above were unsuccessful but use of platinum oxide at room temperature and 40 atm. gave in 5 hr. a small yield of **3-*hexahydrobenzamido*-4-*hydroxy*-4-p-*hydroxyphenylbut*-3-*enoic lactone*** (prisms from aqueous ethanol), m. p. 230° (Found: C, 67·9; H, 6·6; N, 4·6. $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·3; N, 4·65%). This substance on hydrolysis with concentrated hydrochloric acid gave *cyclo*hexanecarboxylic acid, ammonium chloride, and an unidentified ketone. To remove the benzoyl group, 3-benzamido-4-hydroxy-4-*p*-hydroxyphenylbut-3-enoic lactone (1 g.), dissolved in 3N-sodium hydroxide (5 ml.), was cooled in ice-water, and 2·5% sodium amalgam (50 g.) was added with stirring during 1 hr. Benzaldehyde was identified in the solution as its dinitrophenylhydrazone. After acidification, the precipitated solid was removed and recrystallised from ethanol. **3-*Amino*-4-*hydroxy*-4-p-*hydroxyphenylbut*-3-*enoic lactone*** (prisms) (0·3 g.) had m. p. 229° (decomp.) (Found: C, 62·4; H, 4·9; N, 7·6. $C_{10}H_9O_3N$ requires C, 63·0; H, 4·7; N, 7·4%). Its colour with ferric chloride was yellow, and it gave a positive Millon's test and was precipitated by mercuric sulphate and mercuric chloride solutions.

3-*Acetamido*-4-p-*hydroxyphenylbut*-3-*enoic lactone*, prepared by dissolving the amine in a few ml. of acetic anhydride containing a drop of concentrated sulphuric acid, crystallised from aqueous ethanol in prisms, m. p. 250° (decomp.) (Found: C, 61·5; H, 4·8; N, 5·9. $C_{12}H_{11}O_4N$ requires C, 61·8; H, 4·7; N, 6·0%).

Reaction with m-*Acetoxybenzoic Anhydride.*—*m*-Acetoxybenzoic anhydride (1 g.) and benzoylaspartic anhydride (2·5 g.) were heated in boiling xylene (20 ml.) until CO_2 evolution had ceased (5 hr.). The gum precipitated on cooling was washed with ether and extracted with sodium hydrogen carbonate solution. The residue of impure 4-m-*acetoxyphenyl*-3-*benzamido*-4-*hydroxybut*-3-*enoic lactone* (0·9 g.) crystallised from aqueous ethanol in prisms, m. p. 135° (Found : C, 67·5; H, 4·6; N, 4·2. $C_{19}H_{16}O_5N$ requires C, 67·6; H, 4·5; N, 4·2%). The crude substance, when treated with 3N-sodium hydroxide, only partly dissolved, the small amount of insoluble residue consisting of 4-m-*acetoxybenzoyl*-4 : 5-*dihydro*-6-*oxo*-2-*phenyl*-1 : 3-*oxazine*, needles, m. p. 176° (Found : C, 67·5; H, 4·7; N, 4·2. $C_{19}H_{15}O_5N$ requires C, 67·6; H, 4·5; N, 4·2%). This substance after hydrolysis and treatment with thiocyanate gave 2-*mercapto*-4-m-*hydroxyphenyl*-5-*glyoxalinylacetic acid*, prisms (from aqueous ethanol), m. p. 300° (decomp.) (Found : C, 53·1; H, 4·0. $C_{11}H_{10}O_3N_2S$ requires C, 52·8; H, 4·0%).

Removal of the acetyl group from the unsaturated lactone was achieved as for the *p*-compound, 3-*benzamido*-4-*hydroxy*-4-m-*hydroxyphenylbut*-3-*enoic lactone* crystallising from aqueous ethanol in prisms, m. p. 201° (Found : C, 68·6; H, 4·3; N, 4·3. $C_{17}H_{13}O_4N$ requires C, 69·1; H, 4·4; N, 4·7%). This was most readily obtained directly from the xylene solution of the original reaction mixture, after extraction with sodium carbonate, by further extraction with 3N-sodium hydroxide.

Hydrogenation of the unsaturated phenol at 40 atm. with platinum black gave a small yield of 3-*hexahydrobenzamido*-4-*hydroxy*-4-m-*hydroxyphenylbut*-3-*enoic lactone*, m. p. 196° (from aqueous ethanol) (Found : C, 68·0; H, 6·1; N, 4·65. $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·3; N, 4·65%).

3-*Benzamido*-4-*hydroxy*-4-*phenylpent*-3-*enoic Lactone.*—Phenylacetic anhydride (5 g.) and benzoylaspartic anhydride (2 g.) were heated in boiling xylene (20 ml.) for 2 hr. After cooling, the *lactone* (1·6 g.) was removed. Recrystallisation from ethyl acetate gave prisms, m. p. 184° (Found : C, 73·7; H, 5·1; N, 4·4. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·1; N, 4·8%).

Reaction with Nicotinic Anhydride.—Nicotinic anhydride (5 g.) (Badgett, *J. Amer. Chem. Soc.*, 1947, **69**, 2231) was heated in boiling xylene (30 ml.) with benzoylaspartic anhydride (2 g.). After 2 hr. the xylene was cooled in ice, and the crystalline precipitate filtered off, washed with ether, and treated with aqueous sodium hydrogen carbonate to remove nicotinic acid. There remained 3-*benzamido*-4-*hydroxy*-4-3′-*pyridylbut*-3-*enoic lactone* (0·8 g.) which on recrystallisation from ethanol, in which it was sparingly soluble, gave prisms, m. p. 234° (block; decomp.) (Found : C, 68·2; H, 4·5; N, 9·8. $C_{16}H_{12}O_3N_2$ requires C, 68·6; H, 4·3; N, 10·0%). The xylene filtrate (above) was extracted with 3N-hydrochloric acid, and the aqueous solution brought to pH 4 by solid sodium hydrogen carbonate. The precipitated *substance* (1·8 g.) recrystallised from aqueous ethanol in needles, m. p. 227° (block) (Found : C, 64·0; H, 4·6; N, 9·9. $C_{16}H_{14}O_4N_2$ requires C, 64·4; H, 4·7; N, 9·4%). The *phenylhydrazone* crystallised from alcohol in needles, m. p. 175° (decomp.) (Found : C, 67·9; H, 5·4; N, 14·8. $C_{22}H_{20}O_3N_4$ requires C, 68·0; H, 5·2; N, 14·4%). The *oxime*, prisms from ethanol, had m. p. 185° (Found : C, 58·6; H, 4·8. $C_{16}H_{15}O_5N_3$ requires C, 58·4; H, 4·6%). Both lactone and acid were unchanged by boiling 3N-hydrochloric acid, but hydrolysis with 20% hydrochloric acid gave benzoic acid, ammonium chloride, and an unidentified ketone.

Reaction with β-*Benzamidopropionic Anhydride.*—β-Benzamidopropionic anhydride (Barker, *J.*, 1954, 317) was crystallised from acetic anhydride–benzene. Benzoylaspartic anhydride (1 g.) was heated with the anhydride (3 g.) in boiling toluene (20 ml.) for 2 hr. and kept overnight. The sticky crystals were washed with dry ether. Extraction with aqueous sodium hydrogen carbonate removed benzoyl-β-alanine, and the 4-β-*benzamidopropionyl*-1 : 3-4 : 5-*dihydro*-6-*oxo*-2-*phenyloxazine* recrystallised from ethyl acetate as needles, m. p. 167° (1·8 g.) (Found : C, 68·0; H, 5·1; N, 8·3. $C_{20}H_{18}O_4N_2$ requires C, 68·5; H, 5·1; N, 8·0%).

This product (4 g.) was boiled with concentrated hydrochloric acid for 2 hr., then cooled, and the benzoic acid removed by filtration. On concentration of the filtrate under reduced pressure, a small amount of 3 : 6-*dibenzamido*-4-*oxohexanoic acid* separated. It crystallised from ethyl acetate in needles, m. p. 148° (Found : C, 65·3; H, 5·7; N, 7·4. $C_{20}H_{20}O_5N_2$ requires C, 65·2; H, 5·5; N, 7·6%). The mother-liquor on being evaporated *in vacuo* left a gum, which was dissolved in water and treated with potassium thiocyanate on the boiling-water bath. After an hour, crystals of 4-2′-*benzamidoethyl*-2-*mercapto*-5-*glyoxalinylacetic acid* (needles) (2·3 g.) separated. These, on recrystallisation from water, had m. p. 205° (decomp.) (Found : C, 52·5; H, 5·2; N, 12·5. $C_{14}H_{15}O_3N_3S,H_2O$ requires C, 52·0; H, 5·3; N, 13·0%). This substance on further boiling with concentrated hydrochloric acid for 2 hr. give 4-2′-*aminoethyl*-2-*mercapto*-5-*glyoxalinylacetic acid hydrochloride*, m. p. 258° (block) (Found : C, 35·8; H, 5·4.

$C_7H_{11}O_2N_3S$,HCl requires C, 35·4; H, 5·1%). Evaporation of the mother-liquors from the benzamide gave a further quantity of the amine hydrochloride. The free *base* was obtained by adding sodium hydrogen carbonate to the hydrochloride to pH 7, and from water, in which it was rather sparingly soluble, gave prisms, m. p. 300° (decomp.; block) (Found: C, 41·9; H, 5·3; N, 20·2. $C_7H_{11}O_2N_3S$ requires C, 41·8; H, 5·5; N, 20·8%).

Reaction with β-Phthalimidopropionic Anhydride.—*β-Phthalimidopropionic anhydride*, prepared by the action of acetic anhydride on the acid, crystallised from benzene–ethyl acetate as prisms, m. p. 168° (Found: C, 62·3; H, 3·2; N, 6·8. $C_{22}H_{16}O_7N_2$ requires C, 62·9; H, 3·8; N, 6·7%). *4 : 5-Dihydro-6-oxo-2-phenyl-4-β-phthalimidopropionyl-1 : 3-oxazine* was obtained in prisms (from ethyl acetate), m. p. 91°, as in the previous case (Found: C, 63·0; H, 4·7; N, 7·2. $C_{21}H_{16}O_6N_2,H_2O$ requires C, 64·0; H, 4·6; N, 7·1%). Hydrolysis with boiling hydrochloric acid for several hours removed benzoic acid, and further evaporation of the filtrate gave a small amount of felted needles consisting of *3-benzamido-4-oxo-6-phthalimidohexanoic acid*, m. p. 216° (from ethyl acetate) (Found: C, 64·0; H, 4·4; N, 7·1. $C_{21}H_{18}O_6N_2$ requires C, 64·0; H, 4·5; N, 7·1%). The mother-liquor from this substance, on treatment as before with thiocyanate, gave *2-mercapto-4-2′-phthalimidoethyl-5-glyoxalinylacetic acid*, m. p. 233° (decomp.) (from aqueous alcohol) (Found: C, 54·1; H, 4·2. $C_{15}H_{13}O_4N_3S$ requires C, 54·3; H, 3·9%), which resisted further hydrolysis.

I thank Mr. J. O. Stevens for technical assistance.

ROYAL FREE HOSPITAL SCHOOL OF MEDICINE,
8 HUNTER STREET, LONDON, W.C.1.

[*Received, May 19th*, 1954.]

Deoxy-sugars. Part XXV. Structure and Reactivity of Anhydro-sugars. Part II.† Derivatives of* 3 : 6-*Anhydro*-D-*mannose*, 3 : 6-*Anhydro*-2-*deoxy*-D-*galactose, and* 3 : 6-*Anhydro*-2-*deoxy*-D-*glucose.*

By A. B. FOSTER, W. G. OVEREND, M. STACEY, and G. VAUGHAN.

[Reprint Order No. 5085.]

Syntheses are described of methyl 3 : 6-anhydro-2-deoxy-α-D-glucopyranoside and -D-galactopyranoside and of the corresponding 4-methyl ether derivatives. Likewise, methyl 3 : 6-anhydro-α- and -β-D-mannopyranoside and their 2 : 4-di-*O*-methyl derivatives have been prepared. The action of acids on these compounds has been studied and the structures of transformation products have been established. Results obtained in this investigation are discussed with reference to the well-known behaviour towards acidic reagents shown by methyl 3 : 6-anhydro-α-D-glucoside and -D-galactoside (cf. *J.*, 1940, 620; 1941, 88).

IT is well known (Ohle and Thiel, *Ber.*, 1933, **66**, 528; Haworth, Jackson, and Smith, *J.*, 1940, 620; Haworth, Owen, and Smith, *J.*, 1941, 88) that alkali treatment of the 6-*O*-toluene-*p*-sulphonyl derivative of methyl α-D-glucoside or -D-galactoside affords methyl 3 : 6-anhydro-α-D-glucoside and methyl 3 : 6-anhydro-α-D-galactoside respectively. This paper outlines methods for the synthesis of corresponding derivatives from 2-deoxy-D-glucose and 2-deoxy-D-galactose since it was of some interest to discover the influence of the 2-deoxy-group on 3 : 6-anhydro-rings. Methyl 3 : 6-anhydro-α- and -β-D-mannopyranoside have also been prepared and their reactions studied.

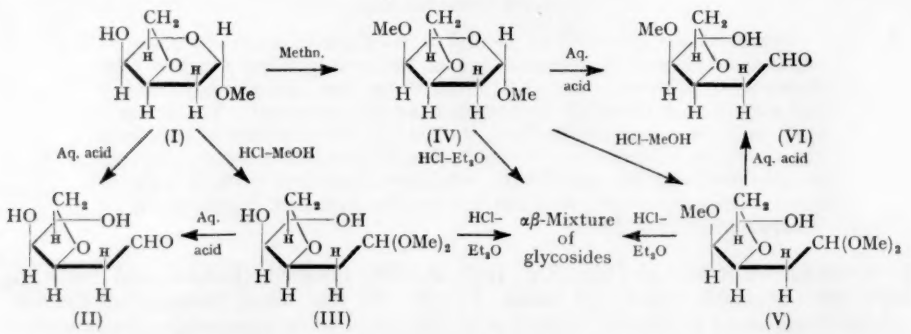
Toluene-*p*-sulphonylation under mild conditions of methyl 2-deoxy-α-D-galactoside afforded syrupy methyl 2-deoxy-6-*O*-toluene-*p*-sulphonyl-α-D-galactoside which was converted into crystalline methyl 3 : 6-anhydro-2-deoxy-α-D-galactoside (I) by sodium hydroxide in ethanol. The anhydro-sugar (I) can be characterised as its crystalline 4-*O*-toluene-*p*-sulphonyl derivative. When the above 6-toluene-*p*-sulphonate was heated with sodium

* Part XXIV, *J.*, 1952, 3608. † Part I, *J.*, 1953, 3308.

iodide in dry acetone, an exchange reaction occurred and sodium toluene-*p*-sulphonate (80%) was precipitated. The conditions were such that an exchange reaction would be expected only with primary toluene-*p*-sulphonyloxy-groups. This evidence coupled with the conversion of the toluene-*p*-sulphonyl derivative into the stable 3 : 6-anhydro-compound (I) indicated that toluene-*p*-sulphonylation of methyl 2-deoxy-α-D-galactoside occurred at position 6, and it follows that the configuration of (I) was correctly assigned.

Similarly, methyl 2-deoxy-α-D-glucoside (Hughes, Overend, and Stacey, *J.*, 1949, 2846) was converted into methyl 3 : 6-anhydro-2-deoxy-α-D-glucoside (VII), and methyl 3 : 6-anhydro-α-D-mannopyranoside (XVIII) was formed from methyl α-D-mannopyranoside. Heating methyl α-D-mannopyranoside with methanolic hydrogen chloride converted it into methyl αβ-D-mannopyranoside from which the β-isomer was isolated as the 2 : 3 : 4 : 6-tetra-acetate. Deacetylation afforded methyl β-D-mannopyranoside which was converted in poor yield into the 3 : 6-anhydro-derivative (XIX). It was best isolated as its 2 : 4-di-*O*-methyl derivative (XX).

On treatment with dilute sulphuric acid at room temperature, the galactose derivative (I) was rapidly hydrolysed and 3 : 6-anhydro-2-deoxy-D-galactose was formed. The properties of this indicate that it exists in the open-chain (*aldehydo*-)form (II) and in this respect it resembles 3 : 6-anhydro-D-galactose (Haworth, Jackson, and Smith, *loc. cit.*). The anhydro-galactoside (I) was hydrolysed much more rapidly than was methyl 2-deoxy-α-D-galactoside (cf. Foster, Overend, and Stacey, *J.*, 1951, 974), and so presumably introduction into the latter molecule of a hydrofuran ring causes considerable strain. Scission of the pyran ring also occurred when (I) was treated with an excess of methanolic hydrogen chloride : 3 : 6-anhydro-2-deoxy-D-galactose dimethyl acetal (III) was formed. Acidic reagents rapidly hydrolysed the acetal (III) to the aldehyde (II), while ethereal or chloroformic hydrogen chloride transformed it into an αβ-mixture of the methyl 3 : 6-anhydro-2-deoxy-D-galactopyranosides. Attempts to prepare 3 : 6-anhydro-2-deoxy-D-galactono-γ-lactone were unsuccessful. Bromine readily oxidised the *aldehydo*-sugar (II) to a galactonic acid derivative which could not be lactonised, a result which is not surprising, since the 4-hydroxyl group is sterically hindered in the 3 : 6-anhydro-galactose series (cf. Haworth, Owen, and Smith, *loc. cit.*).

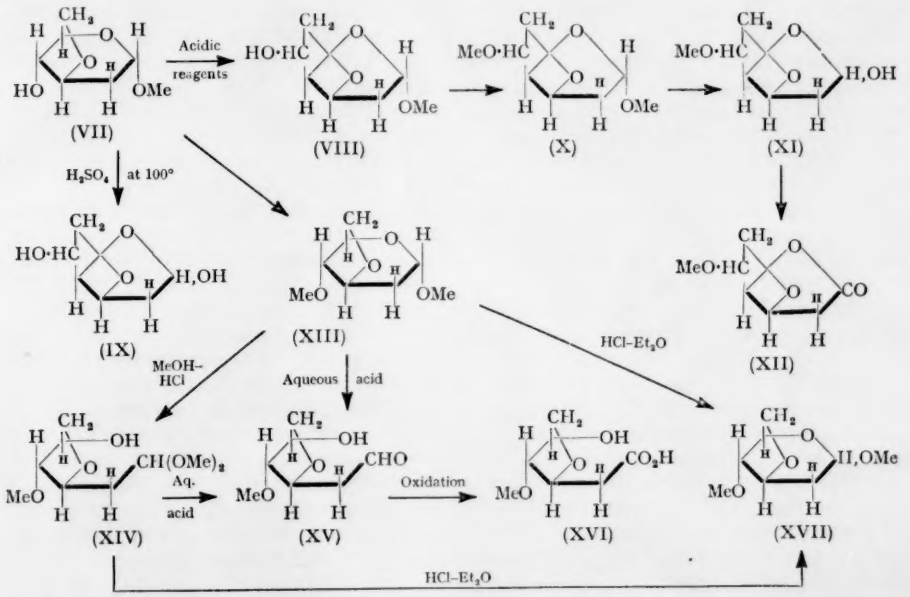


Methylation of the anhydro-galactoside (I) yielded the 4-methyl ether (IV), which was hydrolysed by dilute sulphuric acid at about the same rate as (I), giving 3 : 6-anhydro-2-deoxy-4-*O*-methyl-D-galactose (VI). Methanolic hydrogen chloride converted the ether (IV) into the dimethyl acetal (V) which was hydrolysed to the aldehyde (VI) by aqueous acid. Both the galactoside (IV) and the acetal (V) are rapidly changed into methyl 3 : 6-anhydro-2-deoxy-4-*O*-methyl-αβ-D-galactoside by hydrogen chloride in anhydrous ether. From calculations based on Hudson's rules (Hudson, *J. Amer. Chem. Soc.*, 1909, **31**, 66), it seems that the αβ-mixture of glycosides is composed of about 70% of the α- and 30% of the β-isomer. The reactions described closely parallel the results obtained by Haworth and his co-workers (*loc. cit.*) with methyl 3 : 6-anhydro-α-D-galactopyranoside and its 2 : 4-di-*O*-methyl derivative, except that acidic treatment of methyl 3 : 6-anhydro-2 : 4-di-*O*-

methyl-α-D-galactoside and 3 : 6-anhydro-2 : 4-di-*O*-methyl-*aldehydo*-D-galactose gave methyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-β-D-galactoside, whereas with the 2-deoxy-analogues (IV and V) an αβ-mixture of glycosides was formed with the α-isomer as the major component.

The remarkable conversion of α- and β-forms of methyl 3 : 6-anhydroglucopyranoside into the more stable α- and β-methyl 3 : 6-anhydroglucofuranoside with acids (Haworth, Owen, and Smith, *J.*, 1941, 88) has now been found to occur in the corresponding 2-deoxyglucose series; methyl 3 : 6-anhydro-2-deoxy-α-D-glucopyranoside (VII) was isomerised almost instantaneously by hydrogen chloride in methanol or chloroform to methyl 3 : 6-anhydro-2-deoxy-α-D-glucofuranoside (VIII). Under the conditions employed, it is extremely unlikely that the free sugar is formed as an intermediate. The same change (VII ⟶ VIII) can be achieved, but at a slower rate, by use of dilute aqueous sulphuric acid. Acid treatment of the pyranoside (VII) under more drastic conditions affords 3 : 6-anhydro-2-deoxy-D-glucose (IX), the properties of which lead us to believe that it exists in the furanose form. For this reason and also because of the closely similar behaviour of (VII) and methyl 3 : 6-anhydro-α-D-glucopyranoside towards acids, the furanoside (VIII) is considered to have the α-configuration [cf. the change of methyl 3 : 6-anhydro-α-D-glucopyranoside to methyl 3 : 6-anhydro-α-D-glucofuranoside (Haworth, Owen, and Smith, *loc. cit.*)]. The furanose nature of (VIII) was proved by the standard conversions, *e.g.*, the changes (VIII ⟶ X ⟶ XI ⟶ XII). The lactone (XII) was stable in aqueous solution for several days and was thus of the stable 1 : 4(γ)-type, namely, 3 : 6-anhydro-2-deoxy-5-*O*-methyl-D-glucono-γ-lactone, thereby furnishing evidence of the furanose nature of (VIII).

When methyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-α-D-glucoside is treated with acid, a pyranose to furanose conversion is not possible, and Haworth, Owen, and Smith (*loc. cit.*)



demonstrated that the product was the β-glycoside. This change was analogous to that observed with the corresponding compound in the galactose series.

Methyl 3 : 6-anhydro-2-deoxy-4-*O*-methyl-α-D-glucopyranoside (XIII) was converted immediately by anomerisation into an αβ-mixture (XVII) of glycosides by hydrogen chloride in ether or chloroform. From its optical rotation the glycoside mixture apparently con-

tained 55% of (XIII) and 45% of the β-anomer. When the α-glucoside (XIII) was treated with an excess of methanolic hydrogen chloride, 3 : 6-anhydro-2-deoxy-4-*O*-methyl-D-glucose dimethyl acetal (XIV) was formed by fission of the pyran ring : in this respect the glucoside (XIII) and the galactoside (IV) behave analogously. The acetal (XIV) was readily converted by aqueous acid into 3 : 6-anhydro-2-deoxy-4-*O*-methyl-D-glucose (XV) which can also be obtained directly from the glucoside (XIII).

The behaviour of 3 : 6-anhydro-2-deoxy-4-*O*-methyl-D-glucose towards Schiff's reagent indicates that an appreciable amount must be present in the open-chain (*aldehydo*-)form (XV). Oxidation with bromine yielded the gluconic acid (XVI), which did not lactonise [cf. conversion of (XI) into the lactone (XII)], incidentally providing further evidence of the relative stability of furanose derivatives of 3 : 6-anhydrohexoses. Hydrogen chloride in ether converted the acetal (XIV) into the glucoside (XVII), the proportions of the two anomers in the αβ-mixture being approximately the same as from the glucoside (XIII).

From the foregoing account it is aparent that the behaviour of methyl 3 : 6-anhydro-2-deoxy-α-D-glucopyranoside (VII) and its 4-*O*-methyl derivative (XIII) is very similar to that of methyl 3 : 6-anhydro-α-D-glucopyranoside and its 2 : 4-di-*O*-methyl ether. In general the reactions of the 3 : 6-anhydro-2-deoxyhexoses are faster than of the 3 : 6-anhydrohexoses, and in this respect conform to the usual results obtained when reaction rates of hexoses and 2-deoxyhexoses are compared.

To calculate the proportions of α- and β-forms in the mixture (XVII) it is necessary to assume that Hudson's second isorotation rule (*loc. cit.*) is applicable to the methyl 3 : 6-anhydro-2-deoxy-4-*O*-methyl-D-hexosides. This is probable since it can be shown, by calculations based on optical-rotation data reported in the literature, that the rule is applicable to methyl 3 : 6-anhydro-D-hexosides and their 2 : 4-di-*O*-methyl derivatives.

A similar study has been carried out with methyl 3 : 6-anhydro-α- and -β-D-mannopyranoside. Methyl 3 : 6-anhydro-α-D-mannopyranoside (XVIII) is unaffected by 0·1N-sulphuric acid at room temperature, but is converted slowly but in high yield by methanolic hydrogen chloride into methyl 3 : 6-anhydro-α-D-mannofuranoside (XXII), which was prepared by Valentin (*Coll. Czech. Chem. Comm.*, 1934, **6**, 354) by treatment of 3 : 6-anhydro-D-mannofuranose (XXIII) with hydrogen chloride in methanol. We obtained further proof of the furanose nature of the product (XXII) by converting it by the reactions (XXII ⟶ XXIV ⟶ XXV ⟶ XXVI) into a stable lactone of the 1 : 4γ-type. It was 3 : 6-anhydro-2 : 5-di-*O*-methyl-D-mannono-γ-lactone (XXVI), thereby indicating that the initial material (XXII) must have been a methyl 3 : 6-anhydroglycofuranoside.

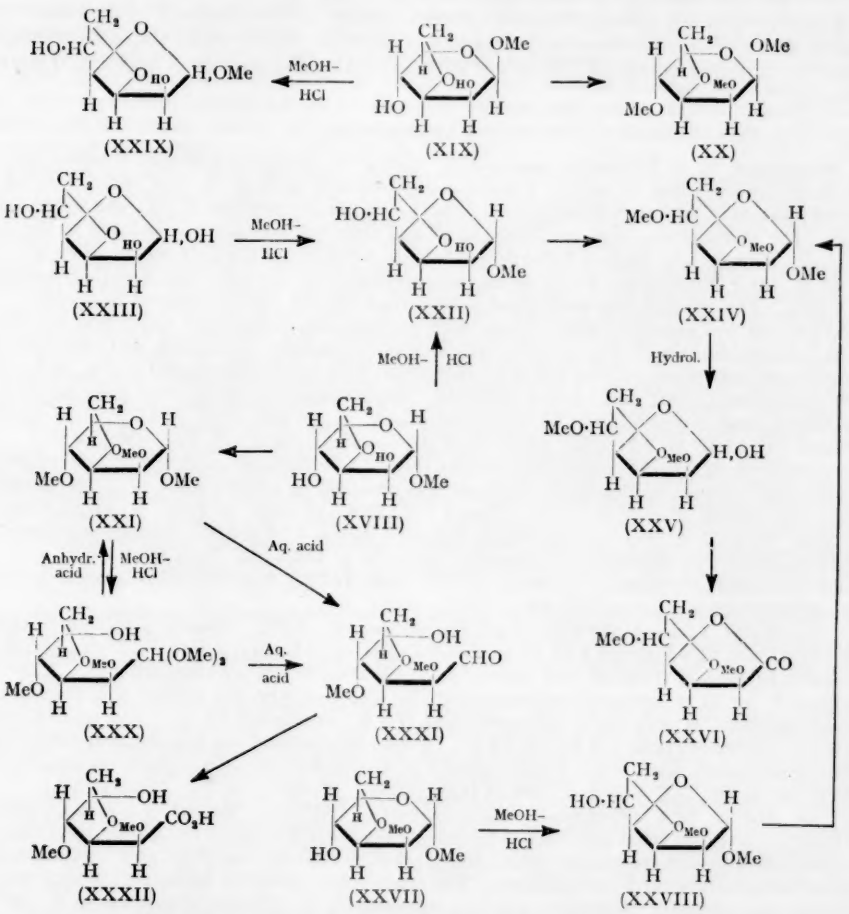
Methyl 3 : 6-anhydro-2-*O*-methyl-α-D-mannopyranoside (XXVII) (Foster, Smith, and Stacey, unpublished work) behaved with methanolic hydrogen chloride analogously to its parent (XVIII) and was converted mainly into the α-furanoside (XXVIII), the structure of which followed from transformation into the 2 : 5-di-*O*-methyl-αβ-pyranoside (cf. XXIV) and thence into the lactone (XXVI). Methyl 3 : 6-anhydro-β-D-mannopyranoside (XIX) on the other hand was rapidly converted by methanolic hydrogen chloride into methyl 3 : 6-anhydro-αβ-D-mannofuranoside (XXIX). Conversion of the β-pyranoside (XIX) into the furanoside is very much faster than that of the α-pyranoside (XVIII) and it appears that the former is therefore under greater strain (for a full discussion see the following paper).

Comparison of these results with those of Haworth, Owen, and Smith (*loc. cit.*) indicates that in the 3 : 6-anhydro-α-D-mannose series the compounds mentioned are under considerably less strain than those in the 3 : 6-anhydro-α-D-glucose series, as is to be expected from the conformational analysis of the various structures (see the following paper). Whereas the β-methyl glycoside of 3 : 6-anhydro-D-mannose is under greater strain than the α-isomer, the opposite is found with derivatives of 3 : 6-anhydro-D-glucose (Haworth, Owen, and Smith, *loc. cit.*).

When the pyranose ⟶ furanose transformation was prevented by using methyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-α- and -β-D-mannopyranoside (XXI and XX respectively) it was found that (*a*) 1% methanolic hydrogen chloride converted the α-anomer (XXI) into a mixture (A) of 3 : 6-anhydro-2 : 4-di-*O*-methyl-*aldehydo*-D-mannose dimethyl acetal (XXX) (*ca.* 67%) and methyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-αβ-D-mannopyranoside (*ca.* 33%), and (*b*) ethereal hydrogen chloride converted the β-anomer (XX) into presumably methyl

3 : 6-anhydro-2 : 4-di-*O*-methyl-αβ-D-mannopyranoside. Addition of acidic reagents under anhydrous conditions to the mixture (A) immediately converted it completely into the α-form (XXI), whereas aqueous acid hydrolysed the acetal grouping and yielded 3 : 6-anhydro-2 : 4-di-*O*-methyl-*aldehydo*-D-mannose (XXXI). The last compound was also prepared from the α-pyranoside (XXI) by aqueous acid: this pyranoside (XXI) was hydrolysed more rapidly than the furanoside analogue (XXIV). The properties of the sugar formulated as (XXXI) indicate that it exists essentially in the open-chain form: oxidation yielded 3 : 6-anhydro-2 : 4-di-*O*-methyl-D-mannonic acid (XXXII) which could not be converted into a lactone.

The product obtained from the β-mannopyranoside (XX) by hydrogen chloride in ether was a non-reducing colourless syrup which partly solidified on nucleation with the α-anomer



(XXI). A comparison of the infra-red spectra of the anomers and this product over the frequency range 700—1010 cm.$^{-1}$ indicates that the reaction product contains a considerable amount of the α-isomer (XXI) (see Table) and so presumably it is an αβ-mixture of methyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-D-mannopyranosides (see Barker, Bourne, Stacey, and Whiffen, *Chem. and Ind.*, 1952, 1156; *J.*, 1954, 171). This slow conversion of the β-glycoside (XX) into the α-glycoside (XXI) under the action of hydrogen chloride in ether is in

good agreement with the result predictable from the concept of non-bonded interactions in the sugar series (following paper).

Compound	Frequencies ($cm.^{-1}$) of absorption peaks								
(XXI)	1003	966	935	901	876	854	811	752	—
(XX) after acid treatment ...	1004	961	935	901	878	856	810	773	751
(XX) before acid treatment ...	997	956	901	892	876	859	826	775	753

Whereas the α-mannopyranoside (XXI) is unaffected by 0·1N-sulphuric acid at room temperature even after 60 hours, the corresponding derivative of methyl 3 : 6-anhydro-α-D-glucoside is completely hydrolysed under these conditions in 8 hours (Haworth *et al.*, *loc. cit.*). This is a further illustration of the greater instability of pyranose derivatives of 3 : 6-anhyro-D-glucose compared with those of 3 : 6-anhydro-D-mannose. In the same way we have the fact that the action of methanolic hydrogen chloride on methyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-α-D-glucopyranoside yields mainly 3 : 6-anhydro-2 : 4-di-*O*-methyl-D-glucose dimethyl acetal, whereas the mannose derivative (XXI) under the same conditions gives the dimethyl acetal (XXX) mixed with a considerable amount of unchanged starting material.

Experimental

Preparation of 3 : 6-*Anhydro-sugars.*—(a) *Methyl* 3 : 6-*anhydro*-2-*deoxy*-α-D-*galactoside* (I). To an ice-cold solution of methyl 2-deoxy-α-D-galactoside (1·80 g.) in dry pyridine (4 ml.), a cooled solution of toluene-*p*-sulphonyl chloride (1·80 g.) in dry pyridine (5 ml.) was added during 1 hr. The mixture was kept for 24 hr. at 0° and then the product was isolated in the usual fashion. The syrupy methyl 2-deoxy-6-*O*-toluene-*p*-sulphonyl-α-D-galactoside {2·10 g.; $[\alpha]_D^{19}$ +79° (*c*, 5·0 in EtOH)} in ethanol (80 ml.) was treated at 60° for 1 hr. with N-sodium hydroxide (6·4 ml.). The solution was neutralised with carbon dioxide and evaporated to dryness. The solid residue was extracted exhaustively with acetone, and the extract was concentrated to a semi-solid residue which was re-extracted with ethyl acetate. Filtration and re-evaporation afforded an amorphous residue which on distillation gave a colourless liquid (0·6 g., 40%), b. p. 120° (bath-temp.)/0·01 mm., which solidified. Recrystallisation from ether gave *methyl* 3 : 6-*anhydro*-2-*deoxy*-α-D-*galactoside* as colourless plates, m. p. 80°, $[\alpha]_D^{15}$ +98° (*c*, 0·78 in H_2O) (Found : C, 52·4; H, 7·7; OMe, 19·8. $C_7H_{12}O_4$ requires C, 52·5; H, 7·5; OMe, 19·4%). This compound (60 mg.) could readily be converted into its 4-O-*toluene*-p-*sulphonyl* derivative (80 mg.) which after recrystallisation from methanol was obtained as a white solid, m. p. 98° (sinters at 88°), $[\alpha]_D^{19}$ +45·6° (*c*, 0·92 in $CHCl_3$) (Found : C, 53·6; H, 5·9; S, 10·2. $C_{14}H_{18}O_6S$ requires C, 53·5; H, 5·7; S, 10·2%). In similar fashion a *methyl* 3 : 6-*anhydro*-2-*deoxy*-αβ-D-*galactoside* (0·22 g., 40%) was obtained as a colourless syrup, b. p. 116—120° (bath-temp.)/0·01 mm., $[\alpha]_D^{19}$ +65° (*c*, 1·5 in H_2O) (Found: C, 52·67; H, 7·7; OMe, 19·7%), from methyl 2-deoxy-6-*O*-toluene-*p*-sulphonyl-αβ-D-galactoside (1·06 g.; $[\alpha]_D^{19}$ +70°).

(b) *Methyl* 3 : 6-*anhydro*-2-*deoxy*-α-D-*glucopyranoside* (VII). Toluene-*p*-sulphonyl chloride (1·532 g.) was added during 1 hr. to an ice-cold solution of methyl 2-deoxy-α-D-glucopyranoside (1·532 g.) (Hughes, Overend, and Stacey, *J.*, 1949, 2848) in dry pyridine (15 ml.). After being kept at 0° for 12 hr. and at room temperature for a further 4 hr. the product was isolated in the usual manner. A solution of the compound (1·5 g.) in ethanol (80 ml.) was treated with N-sodium hydroxide (12 ml.) at 85° for 1·5 hr. A solid resulted and was isolated as described above. Recrystallisation from ether yielded *methyl* 3 : 6-*anhydro*-2-*deoxy*-α-D-*glucopyranoside* (0·5 g., 36%), m. p. 98°, $[\alpha]_D^{20}$ +59·2° (*c*, 2·63 in H_2O) (Found : C, 52·4; H, 7·7; OMe, 19·5%).

(c) *Methyl* 3 : 6-*anhydro*-α-D-*mannopyranoside* (XVIII). Methyl α-D-mannopyranoside (17·62 g.) was converted into its 6-*O*-toluene-*p*-sulphonyl derivative (20 g.) by treatment with toluene-*p*-sulphonyl chloride (17·25 g.) in dry pyridine (200 ml.) for 24 hr. at 0° and thereafter at room temperature for a further hour. The crude ester (20 g.) in ethanol (150 ml.) was converted into methyl 3 : 6-anhydro-α-D-mannopyranoside by allowing it to stand at 0° for 12 hr. and then at 80—85° for 1 hr. with N-sodium hydroxide (75 ml.). The anhydro-compound, isolated as already described, was obtained as colourless crystals (5·0 g.) which after recrystallisation from acetone–ethyl acetate had m. p. 131°, $[\alpha]_D^{15}$ +97° (*c*, 1·4 in H_2O). Valentin (*Coll. Czech. Chem. Comm.*, 1934, **6**, 354) reports m. p. 130—132° and $[\alpha]_D$ +97·1° (in H_2O).

(d) *Methyl* 3 : 6-*anhydro*-β-D-*mannopyranoside* (XIX). In like fashion methyl β-D-mannopyranoside (2·25 g.) was converted *via* its crude 6-toluene-*p*-sulphonate into crude methyl 3 : 6-anhydro-β-D-mannopyranoside (1·0 g.) (A). Attempted distillation of a portion of the

crude syrup (A) (0·4 g.) afforded a small amount of colourless distillate (30 mg., 3·5%), b. p. 160—170° (bath-temp.)/0·01 mm., n^{19} 1·5020, but the main bulk of the material underwent decomposition in the distillation flask. The distillate crystallised on trituration with ethyl acetate, and after recrystallisation from this solvent, *methyl* 3 : 6-*anhydro*-β-D-*mannopyranoside* was obtained having m. p. 103° and $[\alpha]_D^{18}$ −96° (*c*, 0·3 in H_2O) (Found : C, 47·8; H, 7·07; OMe, 18·3. $C_7H_{12}O_5$ requires C, 47·7; H, 6·82; OMe, 17·6%).

The remainder of the syrup (A) (0·6 g.) was methylated twice by the Purdie procedure. Concentration of a chloroform extract of the product gave a dark syrup which distilled as a pale yellow liquid (60 mg.), b. p. 120—130°/0·01 mm., which from elemental analysis was a *methyl* 3 : 6-*anhydromono*-O-*methyl*-β-D-*mannopyranoside* (Found : C, 50·9; H, 7·25; OMe, 33·2. $C_8H_{14}O_5$ requires C, 50·5; H, 7·4; OMe, 32·6%). Further methylation of this liquid by the Freudenberg method yielded *methyl* 3 : 6-*anhydro*-2 : 4-*di*-O-*methyl*-β-D-*mannopyranoside* (20 mg.) as a colourless liquid, b. p. 90—100° (bath-temp.)/0·01 mm., $[\alpha]_D^{20}$ −75° (*c*, 0·4 in MeOH), $[\alpha]_D^{24}$ −70° (*c*, 0·57 in Et_2O) (Found : C, 52·5; H, 8·21. $C_9H_{16}O_5$ requires C, 52·9; H, 7·84%).

The experiment was repeated with 0·97 g. of methyl β-D-mannopyranoside but no attempt was made to isolate methyl 3 : 6-anhydro-β-D-mannopyranoside in pure form. Instead, the crude product was methylated by the Freudenberg method and methyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-β-D-mannoside (0·09 g., 9%) was obtained as a practically colourless liquid, $[\alpha]_D^{24}$ −71° (*c*, 0·6 in Et_2O), n^{27} 1·4553 (Found : C, 52·6; H, 8·2%).

Conversion of Methyl 3 : 6-*Anhydro*-D-*hexopyranosides into the Corresponding Methyl* 3 : 6-*Anhydro*-D-*hexofuranosides.*—(a) *Methyl* 3 : 6-*anhydro*-2-*deoxy*-α-D-*glucofuranoside* (VIII). (1) With 0·1N-sulphuric acid. When 0·1N-sulphuric acid was added at room temperature to methyl 3 : 6-anhydro-2-deoxy-α-D-glucopyranoside (0·262 g.), $[\alpha]_D$ changed from +59·2° to +105° in 12 min. The solution was then neutralised ($BaCO_3$), filtered, and evaporated under diminished pressure to dryness. The residue was extracted with dry methanol and re-evaporation afforded a syrup which on distillation gave *methyl* 3 : 6-*anhydro*-2-*deoxy*-α-D-*glucofuranoside* (0·172 g., 66%) as a colourless liquid, b. p. 100° (bath-temp.)/0·05 mm., n^{19} 1·4745, $[\alpha]_D^{19}$ +111° (*c*, 2·1 in H_2O) (Found : C, 52·5; H, 7·7; OMe, 19·0. $C_7H_{12}O_4$ requires C, 52·5; H, 7·5; OMe, 19·4%).

When methyl 3 : 6-anhydro-2-deoxy-α-D-glucopyranoside (0·6 g.) was heated in 0·1N-sulphuric acid for 1 hr. at 100° the product was 3 : 6-*anhydro*-2-*deoxy*-D-*glucose* (0·38 g., 70%) which was obtained as a colourless syrup, b. p. 120—130° (bath-temp.)/0·05 mm., n^{23} 1·4928, $[\alpha]_D^{20}$ +37·1° (*c*, 1·24 in H_2O) (Found : C, 48·4; H, 7·13. $C_6H_{10}O_4$ requires C, 49·3; H, 6·8%).

(ii) With methanolic hydrogen chloride. Methyl 3 : 6-anhydro-2-deoxy-α-D-glucopyranoside (1·27 g.), dissolved in dry methanol (20 ml.), was treated with 13% methanolic hydrogen chloride (1·0 ml.) at room temperature ($[\alpha]_D$ +60° ⟶ +109° immediately after addition of the acid). Neutralisation with silver carbonate, filtration, removal of the solvent, and distillation gave the product (0·94 g.) as a colourless liquid, b. p. 100° (bath-temp.)/0·05 mm., n^{20}, 1·4744, $[\alpha]_D^{20}$ +112° (*c*, 2·0 in H_2O).

(iii) With chloroformic hydrogen chloride. Essentially similar results were obtained when a dry chloroform solution (1·0 ml.) of the methyl glycopyranoside (10 mg.) was treated with chloroform saturated with dry hydrogen chloride (1 drop). The product had n^{20} 1·4740 and $[\alpha]_D^{20}$ +108° (*c*, 0·5 in H_2O).

(b) *Methyl* 3 : 6-*anhydro*-α-D-*mannofuranoside* (XXII). Methyl 3 : 6-anhydro-α-D-mannopyranoside (0·5 g.) was dissolved in 1% methanolic hydrogen chloride (5·0 ml.). Polarimetric observation indicated that the ensuing reaction was complete in 20 hr. After neutralisation (Ag_2CO_3), filtration, and concentration, the residue was decolorised (charcoal) and then distilled. The colourless distillate (0·4 g.), b. p. 113—115° (bath-temp.)/0·02 mm., crystallised on trituration with ethyl acetate and, after recrystallisation from the same solvent, methyl 3 : 6-anhydro-α-D-mannofuranoside was obtained, having m. p. 86° and $[\alpha]_D^{15}$ +156° (*c*, 0·9 in H_2O) (Found : C, 47·7; H, 6·9. Calc. for $C_7H_{12}O_5$: C, 47·7; H, 6·8%). Valentin (*loc. cit.*) reports m. p. 85° and $[\alpha]_D$ +157°.

(c) *Methyl* 3 : 6-*anhydro*-αβ-D-*mannofuranoside.* A solution of methyl 3 : 6-anhydro-β-D-mannopyranoside [10 mg.; $[\alpha]_D^{18}$ −96° (*c*, 1·0 in MeOH)] in 1% methanolic hydrogen chloride (1·0 ml.) was kept at room temperature for 1 hr. ($[\alpha]_D^{18}$ = +107° after this period) and then neutralised (Ag_2CO_3). Removal of the solvent gave a colourless, non-reducing syrup, $[\alpha]_D^{18}$ +110° (*c*, 1·0 in H_2O), which did not crystallise but became gummy on being seeded with methyl 3 : 6-anhydro-α-D-mannofuranoside. It was *methyl* 3 : 6-*anhydro*-αβ-D-*mannofuranoside* (Found : OMe, 18·1. $C_7H_{12}O_5$ requires OMe, 17·6%).

(d) *Methyl* 3 : 6-*anhydro*-2-O-*methyl*-α-D-*mannofuranoside* (XXVIII). Likewise, treatment of methyl 3 : 6-anhydro-2-*O*-methyl-α-D-mannopyranoside (0·5 g.) with 1% methanolic hydro-

gen chloride afforded *methyl* 3 : 6-*anhydro*-2-O-*methyl*-α(β ?)-D-*mannofuranoside* as a straw-coloured liquid, b. p. 160° (bath-temp.)/0·03 mm., n^{20} 1·4755, $[\alpha]_D^{16}$ +119° (*c*, 0·75 in H_2O) (Found: C, 49·2; H, 7·5; OMe, 31·6. $C_8H_{14}O_5$ requires C, 50·5; H, 7·37; OMe, 32·6%). Purdie methylation of this compound gave methyl 3 : 6-anhydro-2 : 5-di-*O*-methyl-αβ-D-manno-furanoside (XXIV is α-analogue) as a colourless liquid, b. p. 90—95° (bath-temp.)/0·01 mm., n^{15} 1·4612, $[\alpha]_D^{15}$ +178° (*c*, 1·5 in H_2O) (Found: OMe, 46·0%).

Methylation Experiments.—(a) *Methyl* 3 : 6-*anhydro*-2-*deoxy*-4-O-*methyl*-α-D-*galactoside* (IV). Sodium (0·5 g.) was added to a vigorously stirred solution of methyl 3 : 6-anhydro-2-deoxy-α-D-galactopyranoside (1·0 g.) in liquid ammonia (30 ml.), and after 1 hr. methyl iodide (10 ml.) was added during a further hour. Ammonia was removed by aeration and the residue was extracted exhaustively with chloroform. The extract was filtered and evaporated under diminished pressure. The residue was re-extracted with ether, and ethereal solution was concentrated to small bulk, and methanol added. After decolorisation (charcoal) the solution was evaporated and the residue distilled. *Methyl* 3 : 6-*anhydro*-2-*deoxy*-4-*O*-*methyl*-α-D-*galactoside* (0·8 g., 73%) was obtained as a colourless liquid, b. p. 70—74° (bath-temp.)/0·05 mm., n^{19} 1·4650, $[\alpha]_D^{19}$ +81·5° (*c*, 1·78 in H_2O) (Found: C, 55·3; H, 7·98; OMe, 34·9. $C_8H_{14}O_4$ requires C, 55·2; H, 8·05; OMe, 35·6%).

(b) *Methyl* 3 : 6-*anhydro*-2-*deoxy*-4-O-*methyl*-α-D-*glucopyranoside* (XIII). Methyl 3 : 6-anhydro-2-deoxy-α-D-glucopyranoside (1·52 g.) was dissolved in liquid ammonia (20 ml.) containing sodium (1·0 g.) and was methylated with methyl iodide (10 ml.). Stirring was continued for a further 12 hr. and the product was isolated as described for the galactose isomer. *Methyl* 3 : 6-*anhydro*-2-*deoxy*-4-O-*methyl*-α-D-*glucoside* (1·35 g., 82%) was obtained as a colourless liquid, b. p. 96° (bath-temp.)/0·03 mm., n^{19} 1·4626, $[\alpha]_D^{21}$ +58° (*c*, 2·64 in H_2O), which crystallised. After recrystallisation from ether the compound had m. p. 60° and $[\alpha]_D^{20}$ +60° (*c*, 1·2 in MeOH) (Found: C, 55·6; H, 8·12; OMe, 35·1. $C_8H_{14}O_4$ requires C, 55·2; H, 8·05; OMe, 35·6%).

(c) *Methyl* 3 : 6-*anhydro*-2-*deoxy*-5-O-*methyl*-α-D-*glucofuranoside* (X). In similar fashion methyl 3 : 6-anhydro-2-deoxy-α-D-glucofuranoside (0·9 g.) was converted into its 5-O-*methyl* derivative (0·66 g., 65%) which was isolated as a colourless mobile liquid, b. p. 80° (bath-temp.)/0·7 mm., n^{20} 1·4532, $[\alpha]_D^{18}$ +135° (*c*, 2·56 in H_2O) (Found: C, 55·7; H, 8·04; OMe, 35·0%).

(d) *Methyl* 3 : 6-*anhydro*-2 : 4-*di*-O-*methyl*-α-D-*mannopyranoside* (XXI). Methyl 3 : 6-anhydro-α-D-mannopyranoside (2·0 g.), dissolved in a small amount of dry acetone, was methylated twice according to Purdie's procedure. The 2 : 4-di-*O*-methyl derivative (1·6 g., 70%) was obtained as a colourless liquid, b. p. 120° (bath-temp.)/0·2 mm., which crystallised [m. p. 32°; $[\alpha]_D^{20}$ +105° (*c*, 1·1 in H_2O) (Found: OMe, 46·1. Calc. for $C_9H_{16}O_5$: OMe, 45·6%)]. One of us (A.B.F.) had previously prepared this compound in collaboration with Professors M. Stacey and F. Smith, and the substance had m. p. 32—33° and $[\alpha]_D$ +104·1° (*c*, 1·4 in H_2O).

(e) *Methyl* 3 : 6-*anhydro*-2 : 5-*di*-O-*methyl*-α-D-*mannofuranoside* (XXIV). Likewise, Purdie methylation of methyl 3 : 6-anhydro-α-D-mannofuranoside (1·0 g.) afforded the 2 : 5-*di*-O-*methyl* ether (0·8 g., 70%) as a colourless liquid, b. p. 90° (bath-temp.)/0·2 mm., n^{14} 1·4610, $[\alpha]_D^{15}$ +204° (*c*, 0·8 in H_2O) (Found: C, 53·4; H, 7·8; OMe, 45·7. $C_9H_{16}O_5$ requires C, 53·0; H, 7·8; OMe, 45·6%).

Treatments with Methanolic, Ethereal, or Chloroformic Hydrogen Chloride.—(a) *Methyl* 3 : 6-*anhydro*-2-*deoxy*-α-D-*galactoside and its* 4-O-*methyl derivative.* Methanolic hydrogen chloride [1·0 ml. of a 13% (by weight) solution] was added to a solution of methyl 3 : 6-anhydro-2-deoxy-α-D-galactoside (0·327 g.) in dry methanol (10 ml.) ($[\alpha]_D^{19}$ +107° ⟶ +41·6°). The solution was neutralised (Ag_2CO_3), filtered and evaporated under diminished pressure after decolorisation. 3 : 6-*Anhydro*-2-*deoxy*-aldehydo-D-*galactose dimethyl acetal* (III) (0·31 g., 80%) was obtained as a colourless syrup having $[\alpha]_D^{12}$ +18·3° (*c*, 2·9 in H_2O) and n^{20} 1·4755 (Found: OMe, 31·9. $C_8H_{16}O_5$ requires OMe, 32·3%).

Likewise, methyl 3 : 6-anhydro-2-deoxy-4-*O*-methyl-α-D-galactoside (0·295 g.) in methanolic solution (20 ml.) on treatment with 13% methanolic hydrogen chloride (2 ml.) was converted in 60 seconds ($[\alpha]_D$ +93° ⟶ +45°] into 3 : 6-*anhydro*-2-*deoxy*-4-O-*methyl*-aldehydo-D-*galactose dimethyl acetal* (V) (0·19 g., 56%) which was isolated and purified in the usual manner and finally obtained as a colourless non-reducing liquid, $[\alpha]_D^{20}$ +42·3° (*c*, 1·47 in H_2O) (Found: OMe, 44·9. $C_9H_{18}O_5$ requires OMe, 45·1%). When this compound (50 mg.) was treated with ethereal 2·4N-hydrogen chloride (2 drops) it was rapidly converted into methyl 3 : 6-anhydro-2-deoxy-4-*O*-methyl-αβ-D-galactopyranoside, $[\alpha]_D^{19}$ +10° (*c*, 1·0 in H_2O) (Found: OMe, 35·8%). A similar change was effected by chloroformic hydrogen chloride. When methyl 3 : 6-anhydro-2-deoxy-4-*O*-methyl-α-D-galactoside (13·8 mg.) was treated with ethereal hydrogen chloride

(0·17N; 1 ml.) it yielded the corresponding αβ-glycoside in syrupy form, $[\alpha]_D^{19}$ +23·2° (*c*, 1·7 in H_2O) (Found: OMe, 35·3%). During the isolation the solution was evaporated over soda-lime in a vacuum-desiccator and ether (1 ml. portions) was evaporated thrice over the syrupy residue to ensure complete removal of the acid.

(b) 3 : 6-*Anhydro*-2-*deoxy*-aldehydo-D-*galactose dimethyl acetal*. The dimethyl acetal (150 mg.) was treated with ethereal 0·17N-hydrogen chloride (1·0 ml.), and the solution was evaporated over soda-lime *in vacuo* as described above. Distillation of the residue afforded methyl 3 : 6-anhydro-2-deoxy-αβ-D-galactopyranoside (50 mg.) as a colourless oil, b. p. 116—120° (bath-temp.)/0·01 mm., $[\alpha]_D^{19}$ +20° (*c*, 1·6 in H_2O) (Found: OMe, 19 6%).

(c) *Methyl* 3 : 6-*anhydro*-2-*deoxy*-4-O-*methyl*-α-D-*glucoside*. A solution of the named glucoside (0·33 g.) in methanol (5 ml.) was treated with 6% methanolic hydrogen chloride (1 ml.) {$[\alpha]_D$ +60° ⟶ +5·25° exceedingly rapidly}. Neutralisation (Ag_2CO_3), followed by filtration and evaporation of the solution, afforded a residue which on distillation gave 3 : 6-*anhydro*-2-*deoxy*-4-O-*methyl*-aldehydo-D-*glucose dimethyl acetal* (XIV) (0·23 g., 60%) as a colourless liquid, b. p. 100—105° (bath-temp.)/0·05 mm., n^{18} 1·4567, $[\alpha]_D^{19}$ −3·3° (*c*, 1·22 in H_2O) (Found: C, 51·7; H, 8·75; OMe, 44·7. $C_9H_{18}O_5$ requires C, 52·4; H, 8·74; OMe, 45·1%). On treatment of methyl 3 : 6-anhydro-2-deoxy-4-*O*-methyl-α-D-glucoside (74 mg.) in chloroform (5 ml.) with dry hydrogen chloride the specific rotation changed immediately from +55° to −20°. Neutralisation followed by filtration and evaporation gave a colourless non-reducing syrup, $[\alpha]_D^{20}$ −31·7° (*c*, 1·5 in EtOH) (Found: OMe, 35·2%), which partly crystallised when nucleated with the initial material. Application of Hudson's isorotation rule gives a theoretical value of $[\alpha]_D$ −130° for methyl 3 : 6-anhydro-2-deoxy-4-*O*-methyl-β-D-glucoside (cf. p. 3769).

Similarly methyl 3 : 6-anhydro-2-deoxy-4-*O*-methyl-α-D-glucoside (20 mg.) was converted into the αβ-mixture {$[\alpha]_D^{18}$ −30° (*c*, 0·2 in EtOH)} by ethereal 5N-hydrogen chloride (1 ml.). Likewise, methyl 3 : 6-anhydro-2-deoxy-4-*O*-methyl-αβ-D-glucopyranoside, $[\alpha]_D^{19}$ −29° (*c*, 0·5 in EtOH) (Found: OMe, 34·8%), was formed when 3 : 6-anhydro-2-deoxy-4-*O*-methyl-*aldehydo*-D-glucose dimethyl acetal (60 mg.) was dissolved in ethereal 1·7N-hydrogen chloride (1 ml.).

(d) *Methyl* 3 : 6-*anhydro*-2 : 4-*di*-O-*methyl*-α-D-*mannoside*. A solution of the methylated anhydromannoside (0·13 g.) in 1% methanolic hydrogen chloride (5 ml.) was kept at room temperature for 120 hr. and then was worked up in the usual way. A syrup was obtained which from its behaviour and elemental analysis was apparently a mixture of 3 : 6-anhydro-2 : 4-di-*O*-methyl-*aldehydo*-D-mannose dimethyl acetal (*ca.* 67%) and methyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-αβ-D-mannoside (*ca.* 33%) (For the mixture, Found: C, 51·6; H, 7·9; OMe, 49·9%).

When methyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-α-D-mannoside (16·3 mg.) was treated with ethereal 1·7N-hydrogen chloride (2 drops) for 1 min. at room temperature no reaction occurred and the starting material was recovered unchanged. A similar result was obtained when the amount of ethereal hydrogen chloride used was increased (to 1 ml.) and its time of action extended to several hours. Likewise substitution of chloroform for ether was ineffectual in promoting reaction.

(e) *Methyl* 3 : 6-*anhydro*-2 : 4-*di*-O-*methyl*-β-D-*mannoside*. A solution of the mannoside (50 mg.) in dry ether (4 ml.) was treated with ethereal 1·7N-hydrogen chloride (1 ml.). The ensuing reaction, followed polarimetrically, was essentially complete in 14 hr. The product was worked up in the standard fashion and a colourless non-reducing syrup (20 mg.) was obtained. This did not restore the colour to Schiff's reagent, and became gummy on nucleation with methyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-α-D-mannopyranoside. Infra-red spectrographs indicated that the product contained a considerable proportion of methyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-α-D-mannopyranoside.

3 : 6-*Anhydro*-2-*deoxy*-D-*galactose* (II).—An aqueous solution of methyl 3 : 6-anhydro-2-deoxy-α-D-galactoside (0·5 g.) was treated with 2N-sulphuric acid (1 ml.) for 105 min. Thereafter the solution was neutralised ($BaCO_3$), filtered, and evaporated to dryness under reduced pressure. The residue was extracted with water, and the extract evaporated. The syrupy residue was extracted with acetone. Removal of the solvent from this extract afforded a colourless syrup (0·39 g.), n^{15} 1·4977, $[\alpha]_D^{20}$ +23·8° (*c*, 3·61 in H_2O), which readily reduced warm Fehling's solution and rapidly restored the colour to Schiff's reagent. It was most probably 3 : 6-*anhydro*-2-*deoxy*-D-*galactose* (Found: C, 49·1; H, 7·0. $C_6H_{10}O_4$ requires C, 49·3; H, 6·85%).

A similar syrup (0·15 g.), n^{18} 1·4981, $[\alpha]_D^{19}$ +25·5° (*c*, 1·5 in H_2O), was obtained by treating 3 : 6-anhydro-2-deoxy-D-galactose dimethyl acetal (0·29 g.) in water (10 ml.) with N-sulphuric acid (1 ml.) for 4 hr.

3 : 6-*Anhydro*-2-*deoxy*-4-O-*methyl*-D-*galactose* (VI).—Hydrolysis of methyl 3 : 6-anhydro-2-deoxy-4-*O*-methyl-α-D-galactoside (66 mg.) with 0·1N-sulphuric acid (5 ml.) for 30 min. gave

3 : 6-*anhydro*-2-*deoxy*-4-O-*methyl*-D-*galactose* (41 mg.) as a colourless glass, $[\alpha]_D^{20}$ +37·5° (*c*, 1·0 in H_2O) (Found : OMe, 19·7. $C_7H_{12}O_4$ requires OMe, 19·4%). The same compound, $[\alpha]_D^{19}$ +36·5° (*c*, 0·5 in H_2O) (Found : OMe, 19·8%), was prepared by hydrolysis of **3 : 6**-anhydro-2-deoxy-4-*O*-methyl-*aldehydo*-D-galactose dimethyl acetal (130 mg.) with 0·1N-sulphuric acid (5 ml.).

The amorphous material readily reduced warm Fehling's solution and immediately restored the colour to Schiff's reagent.

3 : 6-*Anhydro*-2-*deoxy*-4-O-*methyl*-D-*glucose* (XV).—Hydrolysis of methyl **3 : 6**-anhydro-2-deoxy-4-*O*-methyl-α-D-glucoside (0·53 g.) with 0·1N-sulphuric acid (21 ml.) was complete in 1 hr. The solution was neutralised with barium carbonate, and the product isolated in the usual manner. **3 : 6-*Anhydro*-2-*deoxy*-4-O-*methyl*-D-*glucose*** (0·33 g., 70%) was obtained as a colourless hygroscopic syrup which was reducing towards Fehling's solution and restored the colour to Schiff's reagent in the cold. It had b. p. 126° (bath-temp.)/0·2 mm., n^{15} 1·4717, $[\alpha]_D^{18}$ −24·6° (*c*, 2·36 in H_2O) (Found : C, 51·6; H, 8·15; OMe, 19·0. $C_7H_{12}O_4$ requires C, 52·5; H, 7·5; OMe, 19·4%). The same compound was obtained by hydrolysis of **3 : 6**-anhydro-2-deoxy-4-*O*-methyl-*aldehydo*-D-glucose dimethyl acetal (61 mg.) with 0·1N-sulphuric acid (6 ml.) for 30 min.

Oxidation of this substance (0·12 g.) in water (10 ml.) with bromine (1·0 ml.) for 7 days at 30° yielded **3 : 6-*anhydro*-2-*deoxy*-4-O-*methyl*-D-*gluconic acid*** (XVI) as a pale yellow syrup, b. p. 170° (bath-temp.)/0·01 mm., $[\alpha]_D^{19}$ −21° (*c*, 2 in H_2O) (Found : C, 47·0; H, 7·8. $C_7H_{12}O_5$ requires C, 47·7; H, 6·82%).

3 : 6-*Anhydro*-2-*deoxy*-5-O-*methyl*-D-*glucose*.—Methyl **3 : 6**-anhydro-2-deoxy-5-*O*-methyl-α-D-glucofuranoside (0·51 g.) undergoes slow hydrolysis in 0·1N-sulphuric acid (20 ml.) at room temperature, the change in specific rotation being from +136° to +117° in 15 hr. At 100° the specific rotation changed to +73° during 15 min. and remained constant during further heating. The solution was neutralised and worked up as previously described. **3 : 6-*Anhydro*-2-*deoxy*-5-O-*methyl*-D-*glucose*** (0·24 g., 54%) was obtained as a strongly reducing colourless syrup, b. p. 118° (bath-temperature)/0·05 mm., n^{25} 1·4530, $[\alpha]_D^{20}$ +90° (*c*, 1·7 in H_2O) (Found : C, 52·23; H, 7·2; OMe, 19·1%).

Oxidation of this sugar (170 mg.) in water (10 ml.) with bromine (1 ml.) at 30° for 7 days afforded **3 : 6-*anhydro*-2-*deoxy*-5-O-*methyl*-D-*glucono*-γ-*lactone*** (XII), m. p. 68°, $[\alpha]_D^{18}$ +100° (*c*, 1·44 in H_2O) (const. for 6 days) (Found : C, 52·6; H, 6·17. $C_7H_{10}O_4$ requires C, 53·2; H, 6·33%).

3 : 6-*Anhydro*-2 : 4-*di*-O-*methyl*-aldehydo-D-*mannose* (XXXI).—Methyl **3 : 6**-anhydro-2 : 4-di-*O*-methyl-α-D-mannopyranoside (1·48 g.) was heated at 100° in 0·1N-sulphuric acid (21 ml.). The specific rotation of the substance decreased evenly during 1·5 hr. ($[\alpha]_D$ +104° ⟶ +60°). The solution was neutralised ($BaCO_3$) and the product isolated by the normal procedure. **3 : 6-*Anhydro*-2 : 4-*di*-O-*methyl*-aldehydo-D-*mannose*** was obtained as a colourless syrup (1·1 g., 80%), b. p. 112—116° (bath-temp.)/0·01 mm., n^{19} 1·4845, $[\alpha]_D^{19}$ +57·4° (*c*, 4·39 in H_2O) (Found : C, 49·7; H, 7·5; OMe, 33·0. $C_8H_{14}O_5$ requires C, 50·5; H, 7·4; OMe, 32·6%). An aqueous solution of the compound reduced warm Fehling's solution and rapidly restored the colour to Schiff's reagent.

In like fashion **3 : 6-*anhydro*-2 : 5-*di*-O-*methyl*-D-*mannofuranose*** (XXV) (0·3 g., 50%) was obtained by hydrolysis of an aqueous solution (20 ml.) of methyl **3 : 6**-anhydro-2 : 5-di-*O*-methyl-α-D-mannofuranoside (0·614 g.) with N-sulphuric acid (1·0 ml.), at 100° for 3·5 hr. The product was obtained as a colourless liquid, b. p. 145° (bath-temp.)/0·05 mm., n^{19} 1·4780, $[\alpha]_D^{18}$ +163° (*c*, 1·2 in H_2O) (const. for 2 days) (Found : OMe, 33·2%). The material was strongly reducing to Fehling's solution and slowly restored the colour to Schiff's reagent.

3 : 6-*Anhydro*-2 : 4-*di*-O-*methyl*-D-*mannonic Acid* (XXXII).—**3 : 6**-Anhydro-2 : 4-di-*O*-methyl-*aldehydo*-D-mannose (0·44 g.) was treated with bromine as previously described. Extraction of the product by the usual methods gave **3 : 6-*anhydro*-2 : 4-*di*-O-*methyl*-D-*mannonic acid*** (0·4 g., 84%) as a colourless glass, $[\alpha]_D^{19}$ −10·2° (*c*, 0·6 in H_2O) (Found : OMe, 30·5. $C_8H_{14}O_6$ requires OMe, 30·1%). In an attempt to lactonise the acid (0·2 g.) it was maintained at 150°/0·05 mm. for 2 hr. and then distilled. The straw-coloured distillate, b. p. 180° (bath-temp.)/0·01 mm., $[\alpha]_D^{20}$ −11·0° (*c*, 0·45 in H_2O) (Found : OMe, 30·6%), was unchanged starting material.

3 : 6-*Anhydro*-2 : 5-*di*-O-*methyl*-D-*mannono*-γ-*lactone* (XXVI).—A solution of **3 : 6**-anhydro-2 : 5-di-*O*-methyl-D-mannofuranose (0·2 g.) in water (10 ml.) was oxidised with bromine (1·0 ml.) at 40° for 4 days. Excess of bromine was removed by aeration and hydrogen bromide was eliminated by addition of silver oxide and subsequent filtration. Evaporation afforded a syrupy residue which was extracted with methanol. From this extract a solid material was isolated which on recrystallisation from ethanol gave **3 : 6-*anhydro*-2 : 5-*di*-O-*methyl*-D-*mannono*-γ-*lactone*** (0·19 g., 96%) as colourless crystals, m. p. 118°, $[\alpha]_D^{20}$ +219° (*c*, 0·85 in H_2O) (const. for

2 days) (Found: C, 50·8; H, 6·47; OMe, 32·5. $C_8H_{12}O_5$ requires C, 51·1; H, 6·37; OMe, 33·0%).

Treatment of Methyl 2-Deoxy-6-O-toluene-p-sulphonyl-α-D-galactoside with Sodium Iodide in Acetone.—The toluene-*p*-sulphonyl derivative (0·264 g.) and sodium iodide (0·18 g.) were heated together in acetone solution (2·5 ml.) for 4 hr. at 80—90°. Thereafter the precipitate of sodium toluene-*p*-sulphonate was collected quantitatively in a sintered-glass crucible and was weighed after being washed with acetone and dried. The amount of precipitate (0·125 g.) (uncorrected for solubility losses) corresponded to an 80% exchange of the toluene-*p*-sulphonyloxy-group.

Part of the expenses of this investigation were met by a grant from the Dunlop Rubber Co. Ltd. Thanks are expressed to Mr. R. Stephens and Dr. D. H. Whiffen for the infra-red measurements.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

[*Received, February 3rd,* 1954.]

Electronic Spectra of Some Aromatic Mercury Compounds.

By G. LEANDRI and A. TUNDO.

[Reprint Order No. 5205.]

The absorption spectra of phenyl-, thienyl-, and furyl-mercury derivatives have been measured, and the results correlated with the $-M$ effect shown by mercury substituents. In the case of the thienyl and furyl derivatives, a greater degree of conjugation of the $2p$ electrons of the oxygen than of the $3p$ electrons of sulphur is assumed to be responsible for the more intense bathochromic effect on the primary band in the furyl derivatives.

THE aromatic substituent –Hg–X is linear. The sign of its inductive effect seems to be unknown, but this effect is likely to be weak in any case. However, the mercury atom has two vacant p orbitals in its valency shell and therefore should be able to exert a $-M$ conjugative effect on the aromatic nucleus, although this effect will also be somewhat weak owing to the limitation to orbital overlap imposed by the difference in the principal quantum numbers of the carbon and mercury valency shells. Actually, there is evidence from dipole-moment measurements of such a $-M$ effect (Hampson, *Trans. Faraday Soc.*, 1934, **30**, 877).

TABLE 1. *Ultra-violet spectra (ethanol solutions).**

	C_6H_5X				$X{\cdot}C_6H_4{\cdot}HgCl$				$X{\cdot}C_6H_4{\cdot}Hg{\cdot}C_6H_4X$			
X	$\lambda_{max.}$, mμ	log ε	$\lambda_{max.}$, mμ	log ε	$\lambda_{max.}$, mμ	log ε	$\lambda_{max.}$, mμ	log ε	$\lambda_{max.}$, mμ	log ε	$\lambda_{max.}$, mμ	log ε
H	254·5	2·25	203·5	3·87 (1)	258	2·46 (*a*)	—	—	259 265	3·00 2·79	227	4·40 (*e*)
CH_3	262	2·48	206·5	3·84 (1)	262·5	2·51	224·5	4·10 (*a*)	263	3·27	234	4·73 (*f*)
Cl	264	2·31	209·5	3·87 (1)	264·5	2·43	226	4·23 (*b*)	265	2·94	233	4·56 (*g*)
NO_2	—	—	252	4·00 (2)	—	—	269	4·68 (*c*)	—	—	280	4·66 (*h*)
NH_2	284·5	3·24	234	4·06 (1)	—	—	253	4·13 (*d*)	297	3·99	—	—
$C_6H_5{\cdot}Hg{\cdot}C_6H_4{\cdot}NO_2(p)$	—	—	—	—	—	—	—	—	—	—	273	4·44 (*i*)
ArX = Mesityl	265	2·34	216	3·89 (3)	—	—	—	—	—	—	257	4·01 (*j*)

* Numerals in parentheses refer to spectral data previously recorded; letters refer to preparations.
(1) Doub and Vandenbelt, *J. Amer. Chem. Soc.*, 1947, **69**, 2714. (2) Rodd, "Chemistry of Organic Compounds," Elsevier Publ. Co., 1951, Vol. I-*A*, p. 88. (3) Fehnel and Carmack, *J. Amer. Chem. Soc.*, 1949, **71**, 2932.
(*a*) Nesmejanow, *Ber.*, 1929, **62**, 1013. (*b*) *Idem, ibid.*, p. 1016. (*c*) *Idem, ibid.*, 1934, **67**, 130, 134. (*d*) Otto, *ibid.*, 1902, **35**, 2041. (*e*) *Org. Synth.*, Coll. Vol. I, p. 228. (*f*) Nesmejanow, *Ber.*, 1929, **62**, 1019. (*g*) Under the same conditions as described by Nesmejanow, *ibid.* (*h*) *Idem, ibid.*, p. 1020. (*i*) Freidlina, Nesmejanow, and Kozeschkow, *Ber.*, 1935, **68**, 565. (*j*) Michaelis, *Ber.*, 1895, **28**, 591.

The electronic transitions of benzene, with which we shall compare the transitions now reported for its mercury-substitution products, are the first two singlet (forbidden) transitions. The first, designated in Table 1 by the frequency of its strongest (second)

vibrational maximum, 255 mμ, is well known to belong to a B_{2u} upper state. The nature of the second transition is still under discussion, inasmuch as its upper state could be of either species B_{1u} or E_{2g}. The oscillating electric vectors associated with transitions to

B_{2u}-derived. B_{1u}-derived. E_{2g}-derived.

these states lie in the ring-plane, but otherwise have no prescribed direction. However, when the ring is monosubstituted, or *p*-disubstituted with a group such as HgX, whose bonding direction is an axis of symmetry, the total symmetry drops from D_{6h} to V_h, or C_{2v}, and now the transition derived from the benzene B_{2u} transition becomes polarised perpendicularly to the line of the substituents, while that derived from the B_{1u} or E_{2g}

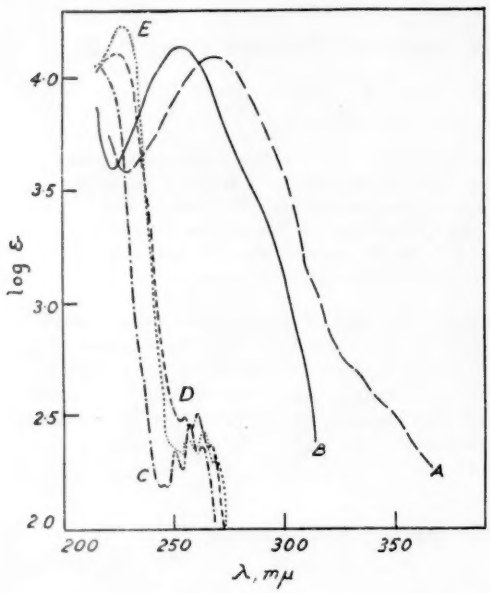


FIG. 1.

A, *p*-NO_2·C_6H_4·HgCl.
B, *p*-NH_2·C_6H_4·HgCl.
C, C_6H_5·HgCl.
D, *p*-CH_3·C_6H_4·HgCl.
E, *p*-Cl·C_6H_4·HgCl.

benzene transition becomes polarised, or contains a component polarised, along that line. Labelling the two transitions (1) and (2) as shown, we can plausibly make the following deductions.

(*a*) Transition (1) should be relatively little affected, while transition (2) might be considerably affected by the chloromercuri-substituent: any observable effect is likely to involve a bathochromic shift with intensification in view of the capacity for conjugation of the substituent, and its comparatively low electronegativity.

(*b*) The introduction into the *p*-position of a second substituent, such as methyl or chloro, which itself interacts only weakly with the benzene chromophore, should scarcely affect transition (1), but might substantially influence transition (2), again in the sense of a bathochromic shift with intensification.

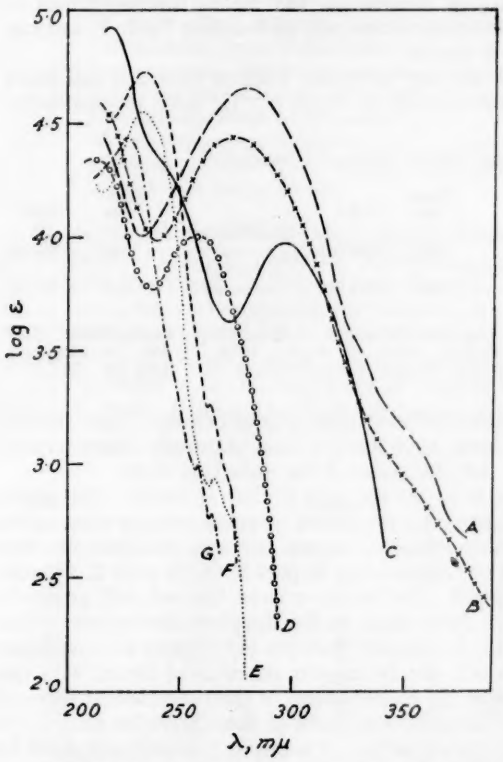
(*c*) A *p*-substituent, such as nitro, which interacts strongly with, and becomes merged in, the benzene chromophore, thereby mixing the characters of the first few benzenoid transitions, should lead to transitions of the combined chromophore, even the first of which should be depressed in frequency and intensified by the chloromercuri-substituent.

(*d*) A *p*-substituent such as amino, which not only merges in the aromatic chromophore, but probably also conjugates through the benzene ring with the mercury atom, should

lead to transitions subject to similar, and possibly more marked, effects of the chloromercuri-substituent.

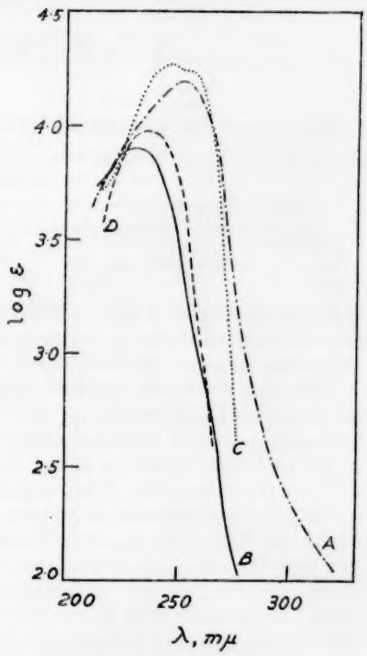
All these points are illustrated in the left-hand and middle divisions of Table 1. For the first transition, the detailed diagrams show, more clearly than does the Table, that, as long as the only substituents are chloromercuri, methyl, and chloro, excitations of the almost pure benzene chromophore are under observation. The vibrational structure of

FIG. 2.



A, $Hg(C_6H_4{\cdot}NO_2\text{-}p)_2$.
B, $B_6H_5{\cdot}Hg{\cdot}C_6H_4{\cdot}NO_2\text{-}p$
C, $Hg(C_6H_4{\cdot}NH_2\text{-}p)_2$.
D, $Hg(mesityl)_2$.
E, $Hg(C_6H_4Cl\text{-}p)_2$.
F, $Hg(C_6H_4{\cdot}CH_3\text{-}p)_2$.
G, $HgPh_2$.

FIG. 3.



A, Di-2-furylmercury.
B, 2-Chloromercurithiophen.
C, Di-2-thienylmercury.
D, 2-Chloromercurifuran.

the benzene B_{2u} system is closely reproduced in the spectra of these derivatives, with similar band separations and intensity variations, thus showing that the ring undergoes almost the same enlargement (about $2\frac{1}{2}\%$) in the upper state, and possesses almost the same internal forces, in the presence of these substituents.

The right-hand division of Table 1 refers to diarylmercury compounds, and requires further comment. To a first approximation these spectra should be similar to those of monoarylmercury compounds, but with a degeneracy derived from the two equivalent chromophores. In second approximation, weak interaction between the chromophores should split the degeneracies, though the split bands might not always be resolved. The splitting should be much greater in transition (2) than in transition (1), for reasons quite similar to those given above for the difference in the sensitivity of the two transitions to the influence by the mercury atom : here we are dealing with their influence on each other,

through the common mercury atom. This major splitting of transition (2) is expected to have three main observable effects on the spectrum. (*a*) One may be able to observe the splitting directly. (*b*) The broadening of transition (2) by splitting, whether resolved or not, will cause it to overlap more with transition (1), and because transition (2) is much the stronger, this will confer on the bands of transition (1) a false appearance of intensification. (*c*) The broadened transition (2) will, on its other side, overlap more with, and will really " steal " more intensity from, what we may call transition (3) in the shorter-wave ultra-violet, a transition which will also be split, and will be still more intense, being derived from the strong (allowed) transition E_{1u} of benzene at 185 mμ. These splittings or broadenings, and the apparent and real intensifications, will be found in Table 1, and can be seen still more clearly on the detailed diagrams.

The effect of mercury substitution on the first electronic band of thiophen and furan has been investigated, with the results summarised in Table 2. In these molecules the

TABLE 2. *Ultra-violet spectra* (*ethanol solutions*).*

	$\lambda_{max.}$, mμ	log ε		$\lambda_{max.}$, mμ	log ε		$\lambda_{max.}$, mμ	log ε
Thiophen	231	3·85 (1)	2-Chloromercuri-thiophen ...	236·5	3·99 (*a*)	Di-2-thienyl-mercury	246	4·26 (*a*)
Furan	<220	(2)	2-Chloromercuri-furan	232	3·91 (*b*)	Di-2-furyl-mercury	252	4·20 (*b*)

* See footnote to Table 1.

(1) Hartough, " Thiophene and Derivatives, The Chemistry of Heterocyclic Compounds," 1952, Interscience Publ., Inc., New York. (2) Raffauf, *J. Amer. Chem. Soc.*, 1950, **72**, 753. (*a*) Steinkoff, *Helv. Chim. Acta* 1952, **35**, 162. (*b*) Gilman and Wright, *J. Amer. Chem. Soc.*, 1933, **55**, 3302.

aromatic system is, of course, fundamentally different from that of benzene; and, indeed, the first excited states of thiophen and furan have not yet been physically characterised. There can, however, be little doubt that they are states of the π-electron shell.

The first electronic band of thiophen is on the red side of that of furan. One might have expected this by analogy with the general convergence of atomic energy states with increasing principal quantum number, inasmuch as the atomic principal quantum numbers of the molecular electrons of the π shell of thiophen are in part 3 and in part 2, whereas those of the π electrons of furan are wholly 2. On the other hand, the red shift produced by mercury substituents is greater in the furan than in the thiophen derivatives. This might also have been expected, because the 3*p* sulphur electrons of thiophen will conjugate less well with 2*p* carbon electrons than will the 2*p* oxygen electrons of furan, with the result that electrons will be less available at the carbon atoms of thiophen than at those of furan, consistently with the well-known chemical differences of these aromatic nuclei. It follow from this that conjugation with a vacant orbital of a mercury substituent must be more effective in the derivatives of furan than in those of thiophen.

EXPERIMENTAL

Carefully purified materials, prepared as indicated in the footnotes to the Tables, were examined with the Beckman D.U. Quartz Spectrometer, a hydrogen lamp being employed as light source. Spectra were taken in solution, of concentration 1 in 10^5, in 95% ethanol, readings being normally 1—2 mμ apart. In the Tables, spectral positions and intensities of characteristic points are expressed in mμ and log ε/mole, respectively.

This work has benefited by an exchange of views with Professor C. K. Ingold, F.R.S., and we thank him for his criticism.

ISTITUTO CHIMICA INDUSTRIALE DELL' UNIVERSITÀ, BOLOGNA. [*Received, March 12th*, 1954.]

Kinetics of the Pyrolysis of Trimethylarsine, Tristrifluoromethylarsine, and Related Compounds.

By P. B. Ayscough and H. J. Emeléus.

[Reprint Order No. 5237.]

A kinetic study of the pyrolysis of trimethyl- and tristrifluoromethylarsine has shown both reactions to be homogeneous and of the first order. They show little difference in activation energy. The main gaseous products are methane, from trimethylarsine, and hexafluoroethane from tristrifluoromethylarsine. Tentative reaction mechanisms based on primary steps involving the liberation of methyl or trifluoromethyl radicals are discussed. The decomposition of trispentafluoroethylarsine is kinetically similar to that of tristrifluoromethylarsine. Preliminary experiments show that the pyrolysis of tristrifluoromethylstibine yields a much higher proportion of unsaturated fluorocarbons.

In the decomposition of simple alkyl-metallic and alkyl-metalloidal compounds the primary step is believed to be the formation of free alkyl radicals. The purpose of the investigation described below was to study kinetically the pyrolysis of trimethyl- and tristrifluoromethylarsine with a view to comparing the reactions of trifluoromethyl radicals with those of the more familiar methyl radicals. Some preliminary work on the pyrolysis of trispentafluoroethylarsine and tristrifluoromethylstibine is also described.

The products of the decomposition of trimethylarsine have not hitherto been examined, although those of the pyrolysis or photolysis of other metal alkyls are known. Table 1

Table 1.

Decomp. temp.	Compound	Products (%) CH_4	C_2H_6	C_2H_4	H_2	Higher hydrocarbons	Ref.
25°	$HgMe_2$ (P)	—	100	—	—	—	1
200	$HgMe_2$ (P)	5	93	—	—	—	1
265	$PbMe_4$ (T)	65	22	2	—	5	2
295	$PbMe_4$ (T)	69	23	2·5	—	4·5	2
302	$HgMe_2$ (T)	71	25	—	—	—	3
340	$PbMe_4$ (T)	86	12	2	0·5	2	2
348	$HgMe_2$ (T)	82	15	—	—	—	3
410	$AsMe_3$ (T)	90	4	2·5	1	2·5	—
485	$SnMe_4$ (T)	88	—	4	6	—	4
550	$PbMe_4$ (T)	29	19	26	22	—	2
659	$SiMe_4$ (T)	58	—	1·5	39	1	5

References: 1, Linnett and Thompson, *Trans. Faraday Soc.*, 1937, **33**, 501; Rebbert and Steacie, *Canad. J. Chem.*, 1953, **31**, 631. 2, Simons, McNance, and Hard, *J. Phys. Chem.*, 1932, **36**, 939. 3, Cunningham and Taylor, *J. Chem. Phys.*, 1938, **6**, 359. 4, Waring and Horton, *J. Amer. Chem. Soc.*, 1945, **67**, 540. 5, Helm and Mack, *ibid.*, 1937, **59**, 60.

summarises the relevant information for methyl derivatives of mercury, lead, tin, and silicon. The symbols (T) and (P) indicate that decomposition was respectively thermal or photochemical. In these reactions the composition of the products varies systematically with the decomposition temperature rather than with the nature of the atom to which the methyl radical is attached. At room temperature the main reaction is dimerisation to ethane but, as the temperature increases, hydrogen-abstraction reactions occur and ethane is progressively replaced by methane. Above 500° ethylene and hydrogen appear in larger quantities, the ethylene suffering polymerisation and decomposition reactions.

Table 1 includes the products of the pyrolysis of trimethylarsine at 410°. The kinetic study of the decomposition of this compound was made at 410—450° and within this range the yields of methane and other products remain approximately the same, namely: methane, 90%; ethane, 4%; ethylene, 2·4%; propylene, 2%; hydrogen 1%. Small amounts of higher hydrocarbons are also formed, together with carbon. All of these

products are believed to be derived directly or indirectly from methyl radicals, the reactions of which are fairly well established (see E. W. R. Steacie, "Atomic and Free Radical Reactions," Reinhold Publ. Corp., New York, 1946).

If it is assumed that trimethylarsine first gives methyl radicals, the low yield of ethane indicates that dimerisation and the abstraction of a methyl radical from an undecomposed molecule of reactant ($CH_3\cdot + AsMe_3 = AsMe_2\cdot + C_2H_6$) are both unimportant. In the early stages of the reaction it is likely that methane may arise from the reaction:

$$CH_3\cdot + AsMe_3 = CH_4 + AsMe_2\cdot CH_2\cdot$$

The subsequent fate of the complex radical $AsMe_2\cdot CH_2\cdot$ is unknown.

At a later stage the abstraction of hydrogen from other hydrocarbons by methyl radicals may become important. The formation of ethylene and hydrogen may be explained by disproportionation reactions such as $2CH_3\cdot = C_2H_4 + H_2$ and $2CH_3\cdot = CH_4 + \cdot CH_2\cdot$, followed by dimerisation of the methylene radicals. Both of these reactions have been postulated by other authors (Helm and Mack, *J. Amer. Chem. Soc.*, 1937, **59**, 60; Waring and Horton, *ibid.*, 1945, **67**, 540) in order to account for the presence of these compounds in the products from the pyrolysis of other organometallic compounds in the same temperature range. Reaction of ethylene with methyl or methylene radicals could give higher saturated or unsaturated hydrocarbons. The decomposition of trimethylarsine in a silica vessel at 400—500° was homogeneous and of the first order with an activation energy of 54·6 kcal./mole. This may be identified with the dissociation energy of the arsenic–carbon bond if it is assumed that the activation energies of secondary reactions in the decomposition are small. A similar argument has been applied in interpreting the activation energies for the thermal decomposition of other alkyl-metallic compounds. The following are typical values: $PbEt_4$ at 245—275°, 36·9 kcal./mole (Meinert, *ibid.*, 1933, **55**, 979); $SiMe_4$ at 659—717°, 78·8 kcal./mole (Helm and Mack, *loc. cit.*); $SiEt_4$ at 520—600°, 50·0 kcal./mole (Waring, *Trans. Faraday Soc.*, 1940, **36**, 1142). These reactions were also of the first order and homogeneous.

The decomposition of tristrifluoromethylarsine in a silica vessel at 350—410° gave 60—90% of hexafluoroethane in the volatile reaction product, corresponding approximately with the reaction $As(CF_3)_3 = As + \frac{3}{2}C_2F_6$, though the pressure increase was somewhat greater than 50%. Up to 10% of perfluoropropane and perfluorobutane were also formed, but no unsaturated fluorocarbons were detected. Most of the residue of the volatile products was a mixture of silicon tetrafluoride and carbon dioxide. These gases made up about 10% of the volatile product from a fresh silica bulb but, with continued use of the bulb, the amount increased and was 20—30% in most of the quantitative runs. Analyses of the products at different stages showed that the proportion of silicon tetrafluoride and carbon dioxide did not vary appreciably during any particular run. These products increased the ratio of the final to the initial pressure. In spite of this complicating factor it was found that, when the total pressure increase was used as a measure of the extent of reaction, the rate constants did not vary appreciably for a given temperature despite considerable differences in the proportions of fluorocarbons and silicon tetrafluoride plus carbon dioxide.

The decomposition of tristrifluoromethylarsine was a first-order reaction and, for the range 350—410°, had an activation energy of 57·4 kcal./mole. If this is identified with the dissociation energy of the carbon–arsenic bond, it is clear that replacement of hydrogen by fluorine causes little change in the bond energy. The nature of the main product is compatible with a primary fission of the carbon–arsenic bond to give a trifluoromethyl radical. Hexafluoroethane could be formed either by dimerisation of trifluoromethyl radicals or by the reaction $CF_3\cdot + As(CF_3)_3 = C_2F_6 + \cdot As(CF_3)_2$. The analytical results show that disproportionation reactions such as $2CF_3\cdot = CF_4 + \cdot CF_2\cdot$ do not occur to a marked extent up to 400°, since no tetrafluoromethane was formed. This reaction predominates in this temperature range for alkyl radicals. There are indications that, in systems containing only fluoroalkyl fragments, carbon–fluorine bonds are not broken to a significant extent below 1000° (Steuenberg and Cady, *J. Amer. Chem. Soc.*, 1952, **74**, 4165). The absence of unsaturated fluorocarbons, particularly tetrafluoroethylene, in the products is

probably linked with the absence of $\cdot CF_2\cdot$ radicals and the very small formation of tetrafluoromethane. An explanation of the production of perfluoropropane and perfluorobutane cannot be based on analogy with the reactions of alkyl radicals since, in the latter, the formation of higher hydrocarbons is always linked with that of unsaturated material.

Some light is thrown on the reaction mechanism by a series of experiments made in a platinum vessel which became available towards the end of the investigation. The result of substituting platinum for silica was to increase the rate constant by about 50%, though the reaction remained of the first order. The composition of the fluorocarbon fraction of the products was however greatly altered (Table 7). In a series of decompositions carried out in vessels of similar size and shape, at the same temperature and pressure (370/300 mm.), C_3 and higher fluorocarbons formed about 10% of the total fluorocarbon from reactions in a silica vessel, and about 37% in a platinum vessel. Arsenic trifluoride was also formed in appreciable amounts in platinum though it was not estimated quantitatively. Very little was formed in silica vessels. In platinum it is possible that $\cdot CF_2\cdot$ radicals may be produced by collision of $CF_3\cdot$ radicals with arsenic, held as arsenide on the platinum surface. If so, reactions such as :

$$\cdot CF_2\cdot + CF_3\cdot \longrightarrow C_2F_5\cdot \longrightarrow C_4F_{10} \text{ and } CF_3\cdot + C_2F_5\cdot \longrightarrow C_3F_8$$

at once became possible. Of these reactions the latter would be more probable, whereas in fact C_3F_8 and C_4F_{10} are found in approximately equal amounts. Small amounts of an inert white polymer, having the characteristics of polytetrafluoroethylene were found in the platinum reaction vessel. This supports the hypothesis that $\cdot CF_2\cdot$ radicals are formed. If monomeric C_2F_4 exists as an intermediate it too could react with $CF_3\cdot$ to give $C_3F_7\cdot$ and C_4F_{10}. In the silica vessel elementary arsenic sublimed rapidly into the delivery tube and was therefore not available to the same extent for the formation of $\cdot CF_2\cdot$ radicals. It is thus possible to form a qualitative picture of the reaction mechanism, though it is clear that side-reactions of this type will greatly complicate the kinetic analysis of the decomposition, particularly in platinum vessels.

The mechanism of formation of silicon tetrafluoride and carbon dioxide is unknown. Direct reaction between tristrifluoromethylarsine and silica is unlikely because the rate-determining step is homogeneous. The gases are probably formed by attack of trifluoromethyl radicals on silica, which is known to occur, even at lower temperatures.

The behaviour of trispentafluoroethylarsine is fundamentally similar. It decomposes at about 280° to give a mixture of fluorocarbons in which perfluorobutane predominates (76%), though the relative amount of higher fluorocarbons (16%) is rather greater than from tristrifluoromethylarsine and there is some unsaturated material in the less volatile fractions. This is not unexpected since the build-up of higher fluorocarbons can take place *via* $\cdot CF_2\cdot$ radicals without, in this case, fission of the strong carbon-fluorine bonds. No hexafluoroethane is produced, so it may be concluded that the disproportionation reaction ($C_2F_5\cdot + C_2F_5\cdot = C_2F_6 + C_2F_4$) does not take place. Silicon tetrafluoride, carbon dioxide, and carbon monoxide are also formed in small quantities. The activation energy of the decomposition is 48 kcal./mole, so that by making the same assumptions as in the case of tristrifluoromethylarsine, a significant weakening of the arsenic-carbon bond can be observed.

The preliminary experiments on the decomposition of tristrifluoromethylstibine at 180—220° show significant differences in the products. The volatile material contains small amounts of tetrafluoroethylene, perfluoro*cyclo*propane, and other unsaturated fluorocarbons containing four or more carbon atoms. Considerable amounts of antimony trifluoride and a polymer resembling polytetrafluoroethylene remained in the silica reaction vessel, and about the same proportion of silicon tetrafluoride and carbon dioxide was produced as in the experiments with tristrifluoromethylarsine. There is insufficient evidence for a detailed consideration of the reaction mechanism, but it is noteworthy that antimony is insufficiently volatile at the reaction temperature to sublime. This therefore raises the possibility of a reaction between trifluoromethyl radicals and antimony leading to the formation of $\cdot CF_2\cdot$, the further reactions of which would probably account for the relatively high yields of unsaturated fluorocarbons.

Experimental

Materials and Methods.—Trimethylarsine was prepared by a modification of the method of Dyke and Jones (*J.*, 1930, 2426). Dry redistilled methyl iodide (175 ml.) in dry *n*-butyl ether (300 ml.) was added from a dropping funnel (3 hr.) to magnesium turnings (60 g.) in *n*-butyl ether (300 ml.). The resulting solution (unfiltered) was treated with arsenic trichloride (75 ml.) in xylene (500 ml.), added dropwise ($2\frac{1}{2}$ hr.). The temperature was kept below 50° and dry nitrogen was passed. The ether layer was syphoned off, the residue extracted with further portions of ether, and the solution distilled. The fraction boiling below 90° was redistilled several times, the sample retained for the pyrolysis experiments (22·3 g.) having b. p. 50·1—50·3° (Found: *M*, 120. Calc. for C_3H_9As: *M*, 120·0). The purity of the sample was confirmed by infra-red spectroscopy.

Tristrifluoromethylarsine was prepared by the method of Brandt, Emeléus, and Haszeldine (*J.*, 1953, 2552). Iodo-compounds were removed by shaking with mercury. Repeated fractional distillation of the residue yielded spectroscopically pure tristrifluoromethylarsine (Found: *M*, 282. Calc. for C_3F_9As: *M*, 281·9).

Trispentafluoroethylarsine and *iodobispentafluoroethylarsine* were prepared by heating pentafluoroiodoethane (30 g.) and arsenic (40 g.) in a steel autoclave for 40 hr. at 230°. Unchanged pentafluoroiodoethane and decomposition products were removed by vacuum-fractionation, and the mixture of arsenicals was distilled at reduced pressure in a small column (Found: As, 17·6; F, 66·0; C_2F_5, 81·1%; *M*, 426; b. p. 96·3°. $C_6F_{15}As$ requires As, 17·4; F, 66·0; C_2F_5, 82·7%; *M*, 432. Found: As, 17·1; F, 42·5; C_2F_5, 54·7; I, 28·6%; *M*, 450; b. p. 120°. $C_2F_{10}IAs$ requires As, 17·1; F, 43·3; C_2F_5, 54·1; I, 28·8%; *M*, 440). Fluorine was estimated by titration in buffered solution with thorium nitrate, the fluoride solution being prepared by heating the arsenical with sodium in a Carius tube at 600°, followed by steam-distillation of the aqueous solution of sodium fluoride with 50% sulphuric acid. C_2F_5 was estimated by hydrolysis with 20% sodium hydroxide solution for 24 hr. at 50°: the pentafluoroethane produced quantitatively in this reaction was distilled and weighed. The solution of sodium arsenite resulting from the hydrolysis was used for the iodometric estimation of arsenic. Iodide was estimated as silver iodide.

The tristrifluoromethylstibine used was prepared by J. W. Dale by reaction of trifluoroiodomethane with antimony in a steel autoclave at 175—185°.

The horizontal tube furnace (5 cm. in diameter), used in the pyrolysis experiments, had 5 independently controlled heating coils. At 400° the variation in temperature along the axis over a length of 30 cm. was $<0·5°$. Overall temperatures were maintained, within $\pm 0·5°$ by manual control. Reaction vessels of silica and of platinum were used (length, 20—25 cm.; int. diam., 3 cm.; capacity, 170—180 ml.). These were connected to the manometric system by a long narrow tube fitted with a ground joint. The dead space was about 3 ml. Capillary manometers were used in pressure measurements. Mercury was used as the manometric fluid, it having been previously established that the reactants and their pyrolysis are unaffected by the presence of mercury in the system. An auxiliary vessel of 300-ml. volume was incorporated in the apparatus for measuring the reactants manometrically. Other attachments were a Töpler pump, a McLeod gauge, and a series of traps for removing reaction products for analysis. Temperatures were measured with a calibrated chromel–alumel thermocouple.

The gas to be decomposed was admitted to the previously evacuated auxiliary vessel, its temperature and pressure were measured, and a tap leading to the reaction vessel was opened for 10 sec. The course of the reaction was followed manometrically, this procedure being justified in each case by a series of analyses of the mixture present at various stages of the decomposition.

Analytical Methods.—The non-condensable gases found in the pyrolysis of trimethylarsine were removed with the Töpler pump and measured. At the same time condensable gases were separated in traps cooled in liquid nitrogen. The non-condensable gases, which contained only methane and hydrogen, were analysed in an Ambler apparatus. The condensable gases were passed through a trap cooled to −80° to remove unchanged arsenicals, pumped off with the Töpler pump, measured, and transferred to the gas-analysis apparatus. Unsaturated hydrocarbons were absorbed in oleum, and the small volume of saturated hydrocarbons remaining was burnt in oxygen to find the average C and H content. The results of these analyses were confirmed and amplified by a mass-spectrographic analysis for which the authors are indebted to Dr. Bradford of Imperial Chemical Industries Limited, Billingham Division.

The decomposition products from fluoroalkyl compounds were distilled into an auxiliary

vessel fitted with a trap cooled in liquid air. Any non-condensable gases were removed with the Töpler pump and measured. The condensable material was then transferred to a molecular-weight bulb fitted with a cold finger for the determination of weight and average molecular weight. This material was further separated in the vacuum system. Unchanged reactant was removed by distillation through a trap cooled to a suitable temperature and the material was divided into two or more fractions by distillation. The acid gases (SiF_4, CO_2) were removed from the most volatile fraction by shaking them with 20% aqueous sodium hydroxide, the weight and molecular weight of the remaining fluorocarbons being measured after removal of water vapour. For confirmation of the identity of the fluorocarbons, infra-red spectra of the various fractions were observed. Comparison of the intensity of characteristic absorption bands of pure fluorocarbons with the intensity of the corresponding bands in the spectra of the mixture enables the composition of the mixture to be estimated. The average molecular weight was also used to estimate the composition of fractions in which only two components were present.

Decomposition of Trimethylarsine.—The reaction was studied between 400° and 460°. In three preliminary experiments, in which the reaction was not allowed to go to completion, it was established that there was an approximately linear relation between the pressure and the amount of unchanged arsenical. This justifies the use of pressure measurements as a means of following the reaction rate. Analyses for hydrogen and methane were made in twenty-one experiments where the reaction was taken to completion. Typical results are shown in Table 2. All volumes are reduced to N.T.P. : Δp is the ratio of the increase in pressure to the initial pressure.

TABLE 2.

Temp.	$AsMe_3$ taken (ml.)	Final vol. (ml.)	Vol. of CH_4 (ml.)	Vol. of H_2 (ml.)	Δp
400°	17·35	36·6	31·0	0·6	1·11
410	13·04	27·5	23·5	0·5	1·10
420	7·96	16·55	14·35	0·25	1·08
440	16·30	34·0	26·7	0·5	1·09
450	16·77	34·7	28·85	0·55	1·06
460	8·24	18·0	13·95	0·25	1·19

Complete analyses by combustion and absorption were carried out on the products from four runs in a silica vessel, with the results given in Table 3, where the volumes of products are also expressed in parentheses as a percentage of the total volatile products. The values given for ethane and ethylene include higher saturated and unsaturated hydrocarbons, respectively. The relative proportions of these as given by the mass-spectrographic analysis of the condensable fraction of the product from a run at 400°, after removal of most of the unchanged arsenical are : CH_4, 0·5; C_2H_4, 27; C_2H_6, 41·0; C_3H_6, 13·0; C_3H_8, 7·0; C_4H_8, 2·0; C_4H_{10}, 0·5; CO_2, 3·0; C_3H_9As, 6·0%. The carbon and hydrogen figures for the saturated hydrocarbons in this

TABLE 3.

Temp.	410°	440°	440°	450°
Vol. (ml.) of : $AsMe_3$	16·95	15·15	8·5	16·30
H_2	0·5 (1·5)	0·5 (1·7)	0·3 (1·9)	0·3 (1·9)
CH_4	30·7 (91·1)	25·7 (87·1)	14·3 (88·4)	—
C_2H_6	1·7 (5·0)	2·2 (7·5)	0·9 (6·0)	—
C_2H_4	0·8 (2·4)	1·1 (3·7)	0·6 (3·7)	—
Total volatiles	33·7	29·5	16·1	30·1
Residual $AsMe_3$	0·8	0·75	0·45	0·75
Total products (obs.)	34·5	30·25	16·55	30·85
Total products (calc.)	35·0	31·95	18·30	33·25

mixture are 2·17 and 6·3 respectively, compared with the average values of 2·1 and 6·2 obtained by combustion. The corresponding figures for the olefin fraction are 2·4 and 4·8. The proportion of olefin is 42%, compared with values between 32 and 39% obtained by absorption in oleum. The calculated value for the total products in Table 3 is based on the observed pressure increase in the reaction. The discrepancy between it and the observed value may be ascribed to operational losses in the analysis and to the presence in the bulb of polymeric material with an appreciable vapour pressure at the reaction temperature. The carbon and hydrogen balance on these runs shows a recovery of 90—95% of the hydrogen and 70—75% of the carbon. Some free carbon was deposited as a coherent layer in the reaction vessel. By using pressure measurements to determine rates the reaction was shown to be of the first order by observing the time

for its quarter and half completion at different initial pressures (Table 4). Specific rate constants are also given.

In three experiments at 450° in the unpacked vessel rate constants of 7·23, 7·41, and 7·03 × 10^{-4} sec.$^{-1}$ were observed, while in a vessel packed with silica powder to give a 10—20-fold increase in surface the value was 6·85 × 10^{-4} sec.$^{-1}$. Similarly at 420° values were 1·32 and 1·31 × 10^{-4} (unpacked) and 1·35 and 1·35 × 10^{-4} (packed) sec.$^{-1}$. These runs were made at an initial pressure of 100 mm. There was no observable change in the products from reactions in packed vessels.

TABLE 4.

Temp.	Initial pressure (mm.)	$t_{\frac{1}{4}}$ (min.)	$t_{\frac{1}{2}}$ (min.)	Rate const. (10^{-4} sec.$^{-1}$)
450°	54·7	7·6	15·4	6·51
	57·2	7·3	16·3	6·86
	97·8	7·0	15·3	7·41
	100·0	6·8	15·9	7·23
	199·5	6·4	13·9	8·09
440	100·3	10·9	23·6	4·29
	101·8	10·3	24·0	4·38
	192·9	10·3	22·8	4·59

The activation energy for the reaction was calculated from initial rates (the first 10—15%) in the range 400—460° at an initial pressure of 100 mm. The results, summarised in Table 5, yield an activation energy of 54·6 ± 1·8 kcal./mole [$\log_{10} k = 12{\cdot}77 - (54{,}600/2{\cdot}303\boldsymbol{R}T)$]. The frequency factor is approx. 10^{13} sec.$^{-1}$, a characteristic value for unimolecular bond dissociation processes.

TABLE 5.

Temp.	Rate constant (10^{-4} sec.$^{-1}$)	Temp.	Rate constant (10^{-4} sec.$^{-1}$)	Temp.	Rate constant (10^{-4} sec.$^{-1}$)
460°	11·2, 11·0	430°	2·275, 2·15, 2·24	410°	0·750, 0·791
450	7·23, 7·48, 7·03	420	1·32, 1·31	400	0·427, 0·420
440	4·29, 4·38				

Decomposition of tristrifluoromethylarsine.—The reaction was studied in the range 350—410° in silica and platinum reaction vessels. The main volatile product in silica was hexafluoroethane, but perfluoropropane and perfluorobutane, detected by examining the infra-red absorption spectra of the less volatile material, were present in approximately equimolecular quantities and constituted about 10% of the fluorocarbon mixture. Distillation of the relatively small quantities of product available proved inadequate for more accurate analysis. No unsaturated fluorocarbons could be detected and only a trace of carbon tetrafluoride was found. A considerable amount of silicon tetrafluoride and carbon dioxide was formed together with a little carbon monoxide. The silica surface became opaque and the rate of attack increased progressively in a series of runs, though this trend was checked by heating the vessel almost to its softening point before use. Table 6 gives typical analyses of the products from successive runs between 360° and 410°, illustrating the wide variation in the ratio, "acid gases": fluorocarbon, and also the effect of strongly heating the vessel (after the run marked with an asterisk). The last two runs were carried out in the presence of silica powder and gave a greatly enhanced proportion of acid gases.

TABLE 6.

Temp.	Total fluorocarbon (g.)	SiF_4 & CO_2 (acid gases) (g.)	Acid gases / Fluorocarbon	Temp.	Total fluorocarbon (g.)	SiF_4 & CO_2 (acid gases) (g.)	Acid gases / Fluorocarbon
400°	0·146	0·014	0·096	360°	0·046	0·026	0·570
,,	0·123	0·020	0·149	,,	0·041	0·024	0·586*
,,	0·148	0·022	0·137	370	0·066	0·015	0·228
390	0·133	0·029	0·218	410	0·058	0·016	0·278
380	0·107	0·023	0·213	390	0·015	0·037	2·46
,,	0·125	0·029	0·247	,,	0·010	0·032	3·20
				400	0·274	0·118	0·480

More detailed analyses were carried out on the combined products from two runs in a silica vessel and from three runs in the platinum vessel, all at 370°. The considerable increase in the relative proportions of higher fluorocarbons is shown in Table 7.

The decomposition was shown to be a first-order reaction by determining the time for a

quarter and the time for half the reaction with various initial pressures. The results are in Table 8, which includes the values of specific rate constants. These too were independant of the initial pressure.

An increase in surface area of 10—20 times caused an increase in the rate constant of about 25% (from $2{\cdot}77 \times 10^{-4}$ to $3{\cdot}44 \times 10^{-4}$ sec.$^{-1}$) while the ratio, acid gases : fluorocarbon, increased from 0·22 to 2·44. According to the method of calculation used by Geddes and Mack (*J. Amer. Chem. Soc.*, 1930, **52**, 4372) this indicates a degree of heterogeneity of not more than 1·5%, despite the very considerable difference in the composition of the products. It is also significant that, when the surface of the vessel was covered with carbon, silver, or with calcium fluoride, there was very little difference in the rate constant, which also remained substantially reproducible throughout a series of experiments in the silica vessel, during which the vessel became very badly etched (see Table 9).

TABLE 7.

Product	Silica vessel g.	Silica vessel %	Platinum vessel g.	Platinum vessel %
CF_4	0·002	0·5	0·004	1·0
C_2F_6	0·246	61·4	0·258	62·4
C_3F_8,C_4F_{10}	0·028	7·0	0·152	36·6
SiF_4,CO_2	0·118	29·4	—	—
CO	0·007	1·7	—	—
	0·401	100·0	0·414	100·0

TABLE 8.

Temp.	Initial press. (mm.)	$t_{\frac{1}{4}}$ (min.)	$t_{\frac{1}{2}}$ (min.)	Rate const. (10^{-4} sec.$^{-1}$)	Temp.	Initial press. (mm.)	$t_{\frac{1}{4}}$ (min.)	$t_{\frac{1}{2}}$ (min.)	Rate const. (10^{-4} sec.$^{-1}$)
400°	51·5	8·5	17·8	5·53	380°	98·0	29·8	80	1·15
,,	102·5	8·9	18·5	5·31	,,	100·1	27·7	74	1·62
,,	197·5	8·1	17·8	5·08	,,	189·3	31·8	83	1·39
390	99·0	16·3	38·5	2·78					
,,	102·4	16·5	35·9	2·75					
,,	193·7	16·2	39·5	2·61					

Specific rate constants were calculated from the mean rate of reaction during the first 10—15% of the decomposition. These values are given in Table 9. The initial pressure was approx. 100 mm. The activation energy in the range 350—410° derived from these values is 57·4 ± 2·9 kcal./mole and the specific rate constant (k) is expressed by the equation $\log_{10} k = 15{\cdot}41 - (57{,}400/2{\cdot}303\,\boldsymbol{RT})$. The frequency factor is higher than normal for unimolecular bond dissociation processes.

TABLE 9.

Temp.	Acid gases / Fluorocarbon	Rate constant (10^{-4} sec.$^{-1}$)	Temp.	Acid gases / Fluorocarbon	Rate constant (10^{-4} sec.$^{-1}$)
410°	0·28	10·8	380°	0·21, 0·21	1·51, 1·62
407	0·25	7·51	370	0·45, 0·23	0·734, 0·708
400	0·28, 0·28, 0·15	5·31, 5·08, 5·35	360	0·56, 0·59	0·356, 0·345
390	0·22, 0·22	2·78, 2·75	350	—	1·63

Decomposition of Trispentafluoroethylarsine.—This compound decomposes at a convenient rate in the range 270—310° but the vapour pressure is too low for accurate kinetic measurements with the manometric system used. For analytical purposes a larger sample was sealed in a silica tube and heated for 12 hr. at 300°. Analysis of the product by distillation gave the following results: C_4F_{10}, 76%; higher fluorocarbons, 16%; SiF_4 and CO_2, 8%; CO, trace; CF_4, trace. Several fluorocarbons, saturated and unsaturated, are present in the less volatile fraction, but they were not identified as comparative infra-red data were not available.

In a preliminary study of the reaction rates the specific rate constants were determined for three decompositions at 280° with an initial pressure of about 25 mm. The values were 2·47, 2·27, and $2{\cdot}33 \times 10^{-4}$ sec.$^{-1}$. If the reaction is of the first order, as is the decomposition of tristrifluoromethylarsine, and has the same frequency factor (approx. 10^{15}), the activation energy is 48·0 kcal./mole.

Decomposition of Tristrifluoromethylstibine.—A convenient temperature range for studying this decomposition is 180—240°, though a complete kinetic study has not been made. Pre-

liminary examination of the products of the reaction show that not more than 50% of the carbon and fluorine in the starting material appears in the volatile products, and of this material 75—80% is silicon tetrafluoride and carbon dioxide. The remaining fluorocarbon is mainly tetrafluoroethylene and perfluoro*cyclo*propane in approximately equimolecular quantities, and some higher olefinic fluorocarbons. No hexafluoroethane or other compound containing CF_3 groups is present. The remainder of the carbon and fluorine appears as antimony trifluoride and a white polymer which behaves like polytetrafluoroethylene (decomposes at 600° in silica, giving mainly tetrafluoroethylene, silicon tetrafluoride, and carbon dioxide).

The pressure–time curves show very considerable irregularities, including, usually, a point of maximum pressure which was followed by a gradual fall in pressure over a period of several hours. These irregularities make it impossible to obtain absolute values of rate constants.

One of the authors (P. B. A.) thanks the Department of Scientific and Industrial Research for a Maintenance Grant.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, March 25th,* 1954.]

αβ-*Unsaturated Aldehydes and Related Compounds. Part V.* Reaction of Acraldehyde with Simple Aliphatic Alcohols. Formation of Acraldehyde Dialkyl Acetals and of β-Alkoxypropaldehydes and their Acetals.*

By R. H. HALL and E. S. STERN.

[Reprint Order No. 5262.]

A re-examination of the acid-catalysed reaction of acraldehyde with restricted amounts of alcohols showed that simple acetals could not be obtained directly in this way in good yield. In particular, Pingert's claims (*Org. Synth.*, 1945, **25**, 1) could not be substantiated (cf. Hall and Stern, *Chem. and Ind.*, 1950, 775), the low-boiling product being β-ethoxypropaldehyde and not acraldehyde diethyl acetal. The use of neutral salts as catalyst was also examined briefly and found unsatisfactory.

Several new acraldehyde acetals, β-alkoxypropaldehydes, and 1 : 1 : 3-trialkoxypropanes were isolated and characterised together with a number of compounds previously imperfectly described.

THE work now reported was undertaken primarily to find an easy method of preparing simple dialkyl acetals of acraldehyde; other, broader, aims were the examination of any differences in reactivity of the aldehyde towards different alcohols and of the nature of the products obtained. A preliminary account of one aspect of this work has already been published (Hall and Stern, *Chem. and Ind.*, 1950, 775).

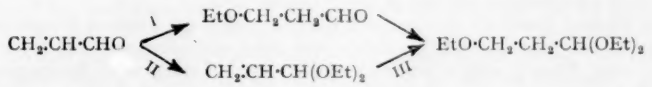
Of the simple dialkyl acetals of acraldehyde only the dimethyl and the diethyl have been described previously. They were accessible by two routes: the reaction of acraldehyde with ethyl orthoformate (Fischer and Baer, *Helv. Chim. Acta*, 1935, **18**, 514), and the dehydrohalogenation of β-halogenopropaldehyde acetals (*e.g.*, Witzemann, Evans, Hass, and Schroeder, *Org., Synth.*, 1931, **11**, 1, 26), neither of which was readily adaptable to large-scale work. More recently, Pingert (*Org. Synth.*, 1945, **25**, 1) claimed that reaction of acraldehyde with a limited amount of ethanol in the presence of hydrogen chloride gave a mixture of acraldehyde diethyl acetal (24—30% yield) and 1 : 1 : 3-triethoxypropane (21—26% yield), separable by fractional distillation. There was no other record, however, of the formation of acraldehyde acetals by the simple, acid-catalysed reaction of acraldehyde and alcohols, a reaction which had earlier been shown to give, with an excess of the alcohol, products such as β-alkoxypropaldehydes, and 1 : 1 : 3-trialkoxypropanes, and, in the presence of sufficient hydrogen chloride, 1 : 1-dialkoxy-3-chloropropanes and 1-alkoxy-1 : 3-dichloropropanes (cf. Alsberg, *Jahresber.*, 1864, 495; Fischer and Giebe, *Ber.*, 1897, **30**, 3056; Wohl, *ibid.*, 1898, **31**, 1797; Witzemann *et al.*, *loc. cit.*; Duliere, *Bull. Soc. chim.*, 1923, [4], **33**, 1650; Voet, *ibid.*, 1927, [4], **41**, 1308; Brabant, *Z. physiol. Chem.*, 1913, **83**, 208; Schulz, U.S.P. 2,288,211).

* Part IV, *J.*, 1954, 2034.

Interest centered initially therefore on a re-examination of Pingert's process, in the hope of obtaining the desired acetal, or an equilibrium mixture of acetal, β-ethoxypropaldehyde, and 1 : 1 : 3-triethoxypropane from which the acetal might be separated. The failure of such experiments to substantiate Pingert's claims has already been reported briefly (Hall and Stern, *loc. cit.*; see also Experimental section): the products were β-ethoxypropaldehyde and 1 : 1 : 3-triethoxypropane. The former, which was mistaken by Pingert for the desired acetal, was an artefact produced from the triethoxy-compound during the distillation, since none was obtained when the reaction mixture was neutralised before distillation.

The 1 : 1 : 3-triethoxypropane obtained could obviously have arisen by two different, possibly reversible, series of reactions (see diagram), but as neither of the intermediates was isolated in significant amounts when the reaction mixture was neutralised before distillation no evidence was forthcoming as to whether one or both of the reaction sequences had operated.

In an attempt to favour reaction II, neutral catalysts for acetal formation (calcium chloride or ammonium chloride) were used, together with a lower concentration of acid catalyst and a reduced ratio (1·5 to 1 molar) of ethanol to aldehyde. Small quantities of acraldehyde acetal were isolated, besides much 1 : 1 : 3-triethoxypropane, despite the fact that reaction III was shown to occur quite readily and almost quantitatively (by treating the acetal with ethanol containing hydrogen chloride). Evidently, in the presence of neutral catalysts and little acid, the rate of acetal formation (reaction II) was somewhat greater than that of its consumption (reaction III) and, at the low conversions attained, some of it remained unattacked.



Catalysis by neutral salts in the absence of acid gave no useful products, possibly because of hydrolysis of any acetal formed in the cold on distillation in the presence of the catalyst. However, azeotropic removal of water from the ammonium chloride-catalysed reaction excluded all possibility of a reversal of the reaction and pure acraldehyde diethyl acetal and 1 : 1 : 3-triethoxypropane (molar ratio 1 to 4) were isolated from the product, although the conversion was poor. Evidently the ammonium chloride was sufficiently acidic to function also as a catalyst for reaction III.

Some evidence for a reaction of type I was obtained by treating acraldehyde with *iso*propanol and sulphuric acid, the product containing β-*iso*propoxypropaldehyde as well as much high-boiling material from which a trace of 1 : 1 : 3-tri*iso*propoxypropane was isolated. No di*iso*propyl acetal of acraldehyde could be detected in the intermediate fractions; this was not altogether surprising as it was known (cf. Adkins and Adams, *J. Amer. Chem. Soc.*, 1925, **47**, 1368) that secondary alcohols formed acetals only with difficulty.

Apart from the use of neutral catalysts, which had already been found unsatisfactory, the potentially most promising ways of favouring reaction II at the expense of I and III involved the use of a higher alcohol [cf. addition of alcohols to acrylic esters (Rehberg, *J. Amer. Chem. Soc.*, 1946, **68**, 544; 1947, **69**, 2966)] and a lower ratio alcohol : acraldehyde. *n*-Propanol and acraldehyde in the presence of sulphuric acid gave a trace of pure dipropyl acetal but the main product was 1 : 1 : 3-tripropoxypropane, and some β-propoxypropaldehyde was also formed. With *n*-butanol and acraldehyde, however, over sulphuric acid and calcium chloride, acraldehyde dibutyl acetal and 1 : 1 : 3-tributoxypropane were obtained in a molar ratio of 4 to 5.

The foregoing qualitative results showed that variation in the experimental conditions and choice of alcohol influenced considerably the course of the reaction. For the preparation of acraldehyde acetals the use of higher alcohols seemed to be particularly advantageous, and this led to an investigation of the reaction of acraldehyde with polyhydric alcohols (to be reported).

The reactivity of α-methylacraldehyde towards ethanol under conditions favouring the formation of the acetal (ammonium chloride catalyst; azeotropic removal of water of reaction) was also examined briefly: the products contained equimolar amounts of α-methylacraldehyde diethyl acetal and 1 : 1 : 3-triethoxy-2-methylpropane. As the ratio was 1 to 4 for acraldehyde, substitution of α-methylacraldehyde had favoured acetal formation (reaction II) at the expense of alcohol addition (reactions I and III); addition of ethanol across the conjugated system of α-methylacraldehyde thus occurred less readily than across that of acraldehyde.

The acraldehyde acetals all showed a characteristic infra-red absorption band at 938 cm.$^{-1}$ and they all readily yielded acraldehyde 2 : 4-dinitrophenylhydrazone; they could thus be differentiated from isomeric structures. Furthermore, the dibutyl acetal on hydrogenation gave propaldehyde dibutyl acetal, identical with an authentic specimen.

The 1 : 1 : 3-trialkoxypropanes were characterised by conversion, under controlled conditions, into the 2 : 4-dinitrophenylhydrazones of the corresponding β-alkoxypropaldehydes, reference samples of which were synthesised where required by the method of Heyse (G.P. 554,949).

The investigation was stopped when an attractive route to the acraldehyde acetals by thermal fission of the 1 : 1 : 3-trialkoxypropanes was discovered (to be reported).

Experimental

Materials.—Acraldehyde was redistilled material of *ca.* 95% purity (determined by analysis for unsaturation by the bromide–bromate method); it contained *ca.* 5% w/w of water and 0·1% w/w of quinol, unless otherwise specified. The quantities of acraldehyde given below all refer to the actual acraldehyde content of the material used.

Acraldehyde Diethyl Acetal (cf. Fischer and Baer, *loc. cit.*).—A mixture of ammonium nitrate (3 g.), ethanol (30 ml.), acraldehyde (1 mole), and ethyl orthoformate (144 g.) was boiled for 8 min., filtered cold, diluted with ether, and washed several times with 2N-ammonia and then with water. The organic layer was dried (K_2CO_3) and fractionated to give acraldehyde diethyl acetal (75 g.), b. p. 63°/91 mm., 59°/75 mm., 55°/65 mm., 26°/13 mm., n_D^{20} 1·4014 (Found: C, 64·95; H, 10·75. Calc. for $C_7H_{14}O_2$: C, 64·6; H, 10·85%). Fischer and Baer (*loc. cit.*) and Witzemann *et al.* (*Org. Synth.*, 1931, **11**, 1) give b. p. 122—125°, but Pingert (*loc. cit.*) gives b. p. 40°/18 mm., 52°/36 mm.; these last b. p.s appear to be too high for the acetal.

β-Ethoxypropaldehyde (cf. Heyse, *loc. cit.*).—Acraldehyde (2 moles) was added dropwise to stirred ethanol (500 ml.) containing 50% w/v aqueous sodium hydroxide (2 ml.) at −5° to −10°. The mixture was acidified with acetic acid (5 ml.) and then with phosphoric acid (1·0 g.), and fractionated, giving β-ethoxypropaldehyde (79·5 g., 40%), b. p. 66—66·5°/67 mm., n_D^{20} 1·4026 (Heyse, *loc. cit.*, gives no physical constants; Schulz and Wagner, *Angew. Chem.*, 1950, **62**, 105, give b. p. 133°; Schulz, U.S.P. 2,288,211, gives b. p. 134°/760 mm., 60°/40 mm.). The *semicarbazone* crystallised from ethyl acetate as needles, m. p. 117° (Found: C, 45·35; H, 8·3; N, 26·5. $C_6H_{13}O_2N_3$ requires C, 45·3; H, 8·25; N, 26·4%), and the 2 : 4-dinitrophenylhydrazone from 60% aqueous ethanol as fine plates, m. p. 85° (Found: C, 46·95; H, 4·9; N, 19·7. Calc. for $C_{11}H_{14}O_5N_4$: C, 46·8; H, 5·0; N, 19·85%). Both derivatives were unknown when first prepared in the course of the work reported here, but subsequently Feazel and Berl (*J. Amer. Chem. Soc.*, 1950, **72**, 2278) found m. p. 84·5—85° (corr.) for the 2 : 4-dinitrophenylhydrazone; they did not succeed in isolating the semicarbazone.

Reaction of Acraldehyde and Ethanol.—Under Pingert's Conditions. In a typical experiment, a solution of hydrogen chloride (2 g.) in ethanol (30 ml.) was added to a mixture of acraldehyde (97% purity; 3 moles) and ethanol (292 ml.) cooled to 0° in an ice-bath. The temperature thereupon rose to 10°; when the ice had melted the mixture was kept for 60 hr. at room temperature. It was then cooled to 5°, partly neutralised with a solution (10—15 ml.) [from sodium (1 g.) in ethanol (25 ml.)], and copper carbonate (1·0 g.) was added. The solution, which was still acid to litmus, was fractionated, giving fractions: (i) ethanol containing about 6% of acraldehyde (77 g.), (ii) b. p. 40—55°/40 mm., n_D^{20} 1·4054 (15—20 g.), (iii) b. p. 30—40°/10 mm., n_D^{20} 1·4026—1·4036 (48 g.), (iv) 1 : 1 : 3-triethoxypropane, b. p. 70°/13 mm., n_D^{20} 1·4070 (91 g.), and a residue (145 g.). A small intermediate fraction (15 g.), b. p. 40—60°/10 mm., n_D^{20} 1·4140—1·4201, was disregarded. In some experiments the sodium ethoxide was omitted and copper carbonate (1·0 g.) only was added. The results were very similar.

Analysis of fraction (i) for acraldehyde by ultra-violet spectrophotometry and for acraldehyde

and its diethyl acetal by oximation and by bromine absorption (bromide–bromate method) showed that no acetal was present.

Dilution of fraction (ii) with carbon tetrachloride caused separation of a very small amount of aqueous phase. This was removed when shaken with anhydrous sodium sulphate. Infra-red examination of the dried solution indicated the presence of β-ethoxypropaldehyde and 1 : 1 : 3-triethoxypropane and the absence of acraldehyde diethyl acetal.

Fraction (iii) was shown to be β-ethoxypropaldehyde by comparison of its infra-red absorption spectrum with that of authentic material; acraldehyde diethyl acetal was absent (no band at 938 cm.$^{-1}$). In confirmation, fraction (iii) gave a 2 : 4-dinitrophenylhydrazone, m. p. 85°, and a semicarbazone, m. p. 117°, identical with the authentic derivatives of β-ethoxypropaldehyde prepared above.

Neutralisation of reaction product. In several experiments sufficient ethanolic sodium ethoxide was added to make phenolphthalein indicator just pink. A small piece (about 0·5 g.) of solid carbon dioxide was then added to bring the solution approximately to neutrality, and the filtered product was fractionally distilled without previous addition of copper carbonate.

In a typical experiment distillation gave: (i) ethanol containing about 0·2% of acraldehyde (101 g.), (ii) a small fraction (2·1 g.), b. p. 48°/200 mm—30°/70 mm., n_D^{20} 1·3660, (iii) a two-phase intermediate fraction (11 g.) b. p. 15—70°/11 mm., (iv) 1 : 1 : 3-triethoxypropane (130 g.), b. p. 70—72°/11 mm., n_D^{20} 1·4065—1·4080, and a residue (181 g.).

Fraction (ii) smelt of acraldehyde acetal, a trace of which (not more than 0·3 g.) may have distilled with the last few drops of ethanol. Fraction (iii) may have contained the water–1 : 1 : 3-triethoxypropane azeotrope.

Catalysis by hydrogen chloride and calcium chloride. Acraldehyde (2 moles) was added rapidly to stirred ethanol (170 ml.), containing hydrogen chloride (0·62 g.) and calcium chloride (15 g.), cooled to 0°. The mixture was stirred at 0° for 0·5 hr., at room temperature for 0·5 hr., and at 50° for 2 hr., and then kept overnight at room temperature. After addition of calcium carbonate (1·7 g.) and filtration, the mixture was rapidly distilled under reduced pressure (loss of acraldehyde and ethanol), and the distillate was fractionated, giving: (i) ethanol (11·5 g.), (ii) impure acraldehyde diethyl acetal (12·7 g.), b. p. 50—55°/70 mm., n_D^{20} 1·4057, and (iii) 1 : 1 : 3-triethoxypropane (101 g.), b. p. 72°/12 mm., n_D^{20} 1·4064.

Catalysis by salts in absence of acid. (*a*) Acraldehyde (1 mole), ethanol (128 ml.), and calcium chloride (5 g.) were stirred at room temperature for 1 hr., at 40° for 2 hr., and then at room temperature overnight. After addition of potassium carbonate (5 g.) the mixture was filtered and rapidly distilled. The distillate contained only acraldehyde and ethanol.

(*b*) A mixture of acraldehyde (2 moles), ethanol (330 ml.; 4 moles), methylene dichloride (100 ml.), and ammonium chloride (6 g.) was refluxed up a 3-ft. Vigreux column fitted with a phase-separating still-head, which removed the upper (aqueous) layer of the distillate and continuously returned the lower layer to the column. After 2 days no more water collected (total volume of aqueous layer, 45 ml.), and the still residues were rapidly distilled. The distillate on fractionation gave pure acraldehyde diethyl acetal (17 g.), b. p. 60°/79 mm., n_D^{20} 1·4012, and 1 : 1 : 3-triethoxypropane (135 g.), b. p. 75°/19 mm., n_D^{20} 1·4067.

Reaction of Acraldehyde Diethyl Acetal with Ethanol.—The acetal (38 g.) was dissolved in ethanol (50 g.), and the solution treated below 3° with ethanol (50 g.) containing hydrogen chloride (1 g.). After several days at room temperature, the solution was made just alkaline with ethanolic sodium ethoxide and the excess of alkali neutralised with solid carbon dioxide. On fractional distillation of the product pure 1 : 1 : 3-triethoxypropane (47 g., 93%) was obtained.

Characterisation of Reaction Products.—(*a*) Acraldehyde diethyl acetal (1 g.) was shaken with 2N-hydrochloric acid (10 ml.) until the solution was homogeneous; addition of a dilute solution of 2 : 4-dinitrophenylhydrazine sulphate in methanol precipitated acraldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 164—165°.

(*b*) 1 : 1 : 3-Triethoxypropane (1·5 g.), b. p. 74°/15 mm., n_D^{20} 1·4068 (Found: C, 61·4; H, 11·2. Calc. for $C_9H_{20}O_3$: C, 61·4; H, 11·45%), was suspended in water (10 ml.) Concentrated hydrochloric acid (3 drops) was added, and the mixture shaken until homogeneous and then treated with a solution of 2 : 4-dinitrophenylhydrazine (2 g.) and sulphuric acid (0·5 ml.) in methanol (25 ml.). The precipitate, on recrystallisation from 60% aqueous ethanol, gave β-ethoxypropaldehyde 2 : 4-dinitrophenylhydrazone as fine plates, m. p. 85°, identical with authentic material (see above). Unless the above procedure was followed closely the derivative was sometimes contaminated with acraldehyde 2 : 4-dinitrophenylhydrazone.

Reaction of Acraldehyde with n-*Propanol.*—In a typical experiment, a mixture of *n*-propanol (300 ml.; 4 moles), acraldehyde (2 moles), and concentrated sulphuric acid (2 g.) was kept over-

night and then neutralised (phenolphthalein) with 5N-sodium hydroxide. Sodium acetate (2 g.) was added and the mixture rapidly distilled under reduced pressure; two major fractions were then obtained, *viz.*, one boiling below 50°/200 mm., the other above 60°/200 mm. The latter on fractional distillation gave, besides unchanged *n*-propanol, a fraction (13 g.), b. p. 52—55°/10 mm., n_D^{20} 1·4145, and pure 1 : 1 : 3-*tri*-n-*propoxypropane* (45 g.), b. p. 113°/15 mm., n_D^{20} 1·4179 (Found: C, 63·3; H, 11·85. $C_{12}H_{26}O_3$ requires C, 66·05; H, 12·0%). The smaller fraction, on repeated refractionation, gave *acraldehyde di*-n-*propyl acetal* (2·4 g.), b. p. 93°/92 mm., n_D^{20} 1·4120 (Found: C, 68·2; H, 11·75. $C_9H_{18}O_2$ requires C, 68·3; H, 11·45%), together with some material which contained β-propoxypropaldehyde (detected by infra-red spectroscopy; for preparation of authentic aldehyde, see Hall and Stern, *J.*, 1952, 4083).

Acraldehyde di-*n*-propyl acetal (0·5 g.) was converted on hydrolysis, in the usual manner, into acraldehyde (characterised as 2 : 4-dinitrophenylhydrazone, m. p. 164—165°). Similarly 1 : 1 : 3-tri-*n*-propoxypropane gave β-*n*-propoxypropaldehyde 2 : 4-dinitrophenylhydrazone, m. p. 100—100·5°, identical with the authentic derivative (*idem*, *loc. cit.*).

Reaction of Acraldehyde with n-*Butanol.*—On mixing of cold *n*-butanol (148 g.; 2 moles) containing concentrated sulphuric acid (0·3 ml.) and calcium chloride (15 g.) with acraldehyde (2 moles), a temperature rise to 40° was observed. The mixture was then kept overnight, dried by addition of calcium chloride (25 g.) and of potassium carbonate (5 g.), filtered, and rapidly distilled under reduced presure. Two fractions were collected, one boiling below and the other above 60°/90 mm. The higher-boiling material on fractional distillation gave, besides a little unchanged *n*-butanol, *acraldehyde di*-n-*butyl acetal* (36 g.), b. p. 84°/13 mm., n_D^{20} 1·4204 (Found: C, 70·9; H, 12·1. $C_{11}H_{22}O_2$ requires C, 70·9; H, 11·9%), and 1 : 1 : 3-*tri*-n-*butoxypropane* (67·2 g.), b. p. 78—80°/0·2 mm., n_D^{20} 1·4258 (Found: C, 69·55; H, 12·15. $C_{15}H_{32}O_3$ requires C, 69·15; H, 12·4%).

Hydrogenation of acraldehyde di-*n*-butyl acetal (5 g.) over 5% palladium–charcoal catalyst (1·0 g.) in ethyl acetate (50 ml.) at room temperature and pressure resulted in the very rapid uptake of hydrogen (97% of theory); fractional distillation of the product gave *propaldehyde di*-n-*butyl acetal* (4·1 g.), b. p. 94°/14 mm., n_D^{20} 1·4128 (Found: C, 70·5; H, 12·75. $C_{11}H_{24}O_2$ requires C, 70·15; H, 12·8%). This was also obtained (40% yield) by keeping overnight a mixture of propaldehyde (58 g.) and *n*-butanol (150 g.) containing concentrated sulphuric acid (0·5 ml.), separating the lower (aqueous) layer, and neutralising, drying, and fractionally distilling the upper layer.

Shaking 1 : 1 : 3-tri-*n*-butoxypropane (1 g.) with water (10 ml.) containing concentrated hydrochloric acid (5 drops) and ethanol (1 ml.) and treating the resulting homogeneous solution with 2 : 4-dinitrophenylhydrazine sulphate in methanol gave β-n-*butoxypropaldehyde* 2 : 4-*dinitrophenylhydrazone* (see below), which crystallised from aqueous ethanol in shiny plates, m. p. 72—73° (Found: C, 50·65; H, 5·75; N, 17·9. $C_{13}H_{18}O_5N_4$ requires C, 50·3; H, 5·85; N, 18·05%).

β-*Butoxypropaldehyde.*—A solution of acraldehyde (2 moles) in *n*-butanol (150 g.) was slowly added to a stirred solution of 50% w/v aqueous sodium hydroxide (2 g.) in *n*-butanol (590 g.) kept at −5° to −10° (acetone–solid carbon dioxide). When addition was complete, the mixture was stirred at −7° for 20 min., acidified with acetic acid (5 ml.) and phosphoric acid (0·56 ml.), and then rapidly distilled. The fraction boiling above 45°/10 mm. on refractionation gave β-butoxypropaldehyde (105 g.; about 48%), b. p. 60°/15 mm., n_D^{20} 1·4156 (Found: C, 64·65; H, 10·7. Calc. for $C_7H_{14}O_2$: C, 64·6; H, 10·85%) (Schulz and Wagner, *Angew Chem.*, 1950, **62**, 105, gave b. p. 146—148°/760 mm. but neither analysed nor characterised the aldehyde).

β-Butoxypropaldehyde gave a 2 : 4-dinitrophenylhydrazone, m. p. 72—73°, identical with that described above (mixed m. p.), and a *semicarbazone*, crystallising from ethyl acetate–light petroleum in long needles, m. p. 97° (Found: C, 51·45; H, 9·1; N, 22·2. $C_8H_{17}O_2N_3$ requires C, 51·35; H, 9·15; N, 22·45%).

Reaction of Acraldehyde and iso*Propanol.*—Acraldehyde (97% purity; 1 mole), *iso*propanol (120 g.; 2 moles), and concentrated sulphuric acid (1·1 ml.) were kept at room temperature for 48 hr. The mixture was then neutralised (phenolphthalein) with 5N-sodium hydroxide, made just acid with acetic acid, and rapidly distilled under reduced pressure; two main fractions were collected, boiling below and above 50°/180 mm., respectively. The higher-boiling material (*ca.* 75 g.) on fractionation gave: (i) β-iso*propoxypropaldehyde* (15—25 g.), b. p. 45°/15 mm., n_D^{20} 1·4048 (Found: C, 62·25; H, 10·65. $C_6H_{12}O_2$ requires C, 62·05; H, 10·4%), (ii) intermediate fractions (*ca.* 20 g.), b. p. 50—95°/15 mm., n_D^{20} 1·410—1·433, (iii) impure 1 : 1 : 3-tri*iso*propoxypropane (7 g.), b. p. 90—97°/11 mm., n_D^{20} 1·4127, and (iv) high-boiling substances (29 g.).

The β-*iso*propoxypropaldehyde [fraction (i)] gave a 2 : 4-*dinitrophenylhydrazone*, plates, m. p. 99° (from aqueous methanol) (Found : C, 48·5; H, 5·4; N, 19·0. $C_{12}H_{16}O_5N_4$ requires C, 48·65; H, 5·45; N, 18·9%), and a *semicarbazone*, needles, m. p. 127·5—128° (from 25% aqueous ethanol) (Found : C, 48·4; H, 8·75; N, 24·2. $C_7H_{15}O_2N_3$ requires C, 48·55; H, 8·75; N, 24·25%).

Refractionation of fraction (iii) gave material (1·5 g.), b. p. 87°/8 mm., n_D^{20} 1·4113, the properties of which approximated to those of authentic 1 : 1 : 3-tri*iso*propoxypropane, b. p. 89°/11 mm., n_D^{20} 1·4096 (Hall, Stern, and the Distillers Co., Ltd., B.P. 695,789; cf. Bellringer, Bewley, and the Distillers Co., Ltd., B.P. Appln. 9689/50). On hydrolysis with dilute hydrochloric acid and treatment with 2 : 4-dinitrophenylhydrazine reagent it furnished β-*iso*propoxypropaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 99°.

Reaction of α-Methylacraldehyde with Ethanol.—A mixture of α-methylacraldehyde (140 g.; 2 moles), ethanol (184 g.; 4 moles), ammonium chloride (6 g.), and methylene dichloride (150 ml.) was rapidly distilled through a 3-ft. Vigreux column fitted with a phase-separating still-head; the upper (aqueous) layer of the distillate was removed and the lower layer continuously returned as reflux. After 8 days, 35 ml. of water had been removed and no more appeared to be formed. The reaction mixture was rapidly distilled (the pressure being progressively reduced) and the material (129 g.) boiling above 80°/750 mm. was fractionated, giving α-methylacraldehyde diethyl acetal (71 g.), b. p. 52°/30 mm., 39°/10 mm., n_D^{20} 1·4081 (oximation equiv., 145. Calc. : equiv., 144), and 1 : 1 : 3-triethoxy-2-methylpropane (84·5 g.), b. p. 74°/10 mm., n_D^{20} 1·4089 (oximation equiv., 188. Calc. : equiv., 190) (cf. Bellringer *et al.*, *loc. cit.*).

Repetition of the above experiment, with hydrogen chloride (0·5 g.) in place of ammonium chloride, gave α-methylacraldehyde diethyl acetal (63 g.) and 1 : 1 : 3-triethoxy-2-methylpropane (76 g.).

The authors are indebted to Dr. H. M. Stanley for his interest in this work, to Mr. A. R. Philpotts and Mr. W. Thain for the determination and interpretation of infra-red absorption spectra, and to the Directors of the Distillers Co., Ltd., for permission to publish this paper.

THE DISTILLERS CO., LTD., RESEARCH AND DEVELOPMENT DEPT.,
GREAT BURGH, EPSOM, SURREY. [*Received, March 30th*, 1954.]

Magnetochemistry of the Heaviest Elements. Part VIII. Metallic Plutonium.*

By J. K. DAWSON.

[Reprint Order No. 5329.]

The magnetic susceptibility of metallic plutonium has been measured up to 350° c. Indications of structure transitions were observed at 119°, 205° and about 300°. The susceptibility of two samples was almost independent of temperature and had the value $2{\cdot}52 \times 10^{-6}$ per g. at 20° for the purest sample. A third sample showed a marked decrease of susceptibility with increase of temperature.

THE magnetic susceptibility of metallic plutonium was examined for two main reasons. First, phase changes in metallic systems are often accompanied by small, but abrupt, changes in the susceptibility–temperature curve and the observation of such a curve for plutonium should give information concerning any transition temperatures occurring within the temperature range investigated. Secondly, comparison of the shape of the susceptibility–temperature curve with similar curves for other metals might give information concerning the electronic state of plutonium.

EXPERIMENTAL

The magnetic susceptibilities were measured by use of the quartz torsion fibre microbalance described by Dawson and Lister (*J.*, 1950, 2177). Each sample was sealed in an argon atmosphere inside a Pyrex capillary. After the measurements had been completed, each sample tube

* Part VII, *J.*, 1952, 2705.

was broken open at a scratch applied with a sharp edge of broken porcelain, the sample was removed, the two halves of the tube were sealed together, and the magnetic effect on the empty tube was determined. Measurements above room temperature were made by surrounding the sample tube with a non-inductively wound furnace and the temperatures were measured by two thermocouples protruding into the furnace tube, one above and one below the sample. The balance was calibrated by using ferrous ammonium sulphate for which the gram-susceptibility at 20° was taken as $32{\cdot}31 \times 10^{-6}$.

Four samples of plutonium obtained from three separate preparations were used. They were in the form of short lengths of extruded wire; details are given in the tables of results. Sample C is regarded as the purest.

Preliminary measurements on sample A indicated that an abrupt increase in the susceptibility at about 120° was reproducible on the heating curves provided that the sample was allowed to remain at room temperature for about 24 hr. between each set of measurements. Considerable hysteresis was observed; in fact, the change of susceptibility appeared to be not less than 60° lower on cooling than on heating. Cooling curves were not investigated in detail, and for samples B and C, heating curves only were observed with the exception that a single measurement on sample B indicated that the second change in susceptibility behaviour was at least 40° lower on cooling.

The complete heating curves on samples B and C were each extended over three days: first day, α-phase; second day, α → β-transition, β-phase; retained in beta-phase overnight, third day, β → γ-transition and higher temperatures.

The results are given in the Tables. The times quoted in the second columns are the intervals during which the sample temperatures were held constant at the values given in the first columns; the magnetic susceptibilities per g. (χ_g) are shown in the final columns.

*The magnetic susceptibility of plutonium.**

Temp.	*t*	$10^6\chi_g$	Temp.	*t*	$10^6\chi_g$	Temp.	*t*	$10^6\chi_g$	Temp.	*t*	$10^6\chi_g$
Sample A. Weight, 6·74 mg. Length 5 mm. Purity, 99·66% excluding oxygen (this sample had a rather thick yellow oxide coating).											
−183°	—	4·20	114°	1	2·62	135°	1	2·70	208°	1	2·66
− 72	—	2·75	116	1	2·65	156	1	2·68	234	0·5	2·57
+ 27	1	2·68	118	1·5	2·68	175	1	2·70	283	0·5	2·56
62	1	2·62	118	2·5	2·70	190	0·5	2·69	294	0·3	2·51
84	1	2·63	125	1	2·69	195	0·5	2·69	304	0·3	2·51
86	2	2·62	127	1	2·69	201	1	2·71	327	0·3	2·52
110	1	2·62	133	0·5	2·70						
Sample B. Weight, 19·84 mg. Length 2·8 mm. Purity, 99·8% excluding oxygen, but no appreciable oxidation visible.											
19	—	5·23	120	1	4·06	185	0·5	2·67	248	0·3	2·26
50·5	0·5	4·90	120	2	4·08	195	0·5	2·52	263	0·3	2·25
79	0·5	4·55	129	1	3·88	196	0·5	2·51	280	0·3	2·24
103	0·5	4·18	143	0·5	3·52	200	0·5	2·40	295	0·3	2·23
110·5	0·5	4·07	155	0·5	3·28	200	1	2·40	304	0·3	2·19
118	1	4·01	166	0·5	3·02	210	0·5	2·33	318	0·3	2·19
120	0·5	4·02	176	0·5	2·80	220	1	2·30	341	0·3	2·19
Sample C. Weight, 20·57 mg. Length 1·6 mm. Purity, 99·87% excluding oxygen (no appreciable oxidation visible).											
20	—	2·52	115·5	1·5	2·49	140	17	2·61	203	0·7	2·59
48	0·5	2·51	117·5	0·5	2·49	167	1	2·61	216·5	0·7	2·52
76·5	0·7	2·51	120	2	2·58	186	1	2·59	239	0·5	2·53
97	1·5	2·50	140	1	2·61	196	0·5	2·59	282	0·5	2·52
101	0·7	2·50									

* *t* = Heating time (hr.).

Discussion

Fig. 1 shows several sharp breaks in the susceptibility–temperature curves. It seems reasonable to associate these changes with the interconversion of different allotropic modifications of the metal. The following table gives the temperatures at which the changes occur and compares them with figures recently quoted for the same transitions determined by other methods. The transition temperatures obtained in this investigation are consist-

ently lower; this may be due to the considerably longer time allowed at each temperature for equilibrium to be established, although heating rates of only 1—2° per min. were used in

Transition temperatures on heating curves (°C).

Transition	Sample	Thermomagnetic	Dilatometric (1)	Dilatometric (2)	Thermal analysis (2)	Electrical resistance (2)
$\alpha \rightarrow \beta$	A	116—118°	136°	135°	140°	135°
	B	118—120				
	C	118—120				
$\beta \rightarrow \gamma$	A	202—208	225	225	235	220
	B	197—200				
	C	204—214				
$\gamma \rightarrow \delta$	A	286—294	320	315	325	325
	B	296—303				
	C	—				

(1) Lord, *Nature*, 1954, **173**, 534. (2) Ball, Robertson, Marden, Lee, and Adams, *ibid.*, p. 535.

the other methods. It is known, however, that these transitions are rather sluggish; for sample B, for instance, the $\alpha \rightarrow \beta$-change required rather more than 2 hr. for completion. The considerable hysteresis effects noted in the Experimental section were also found by

FIG. 1. *The thermomagnetic behaviour of plutonium.*

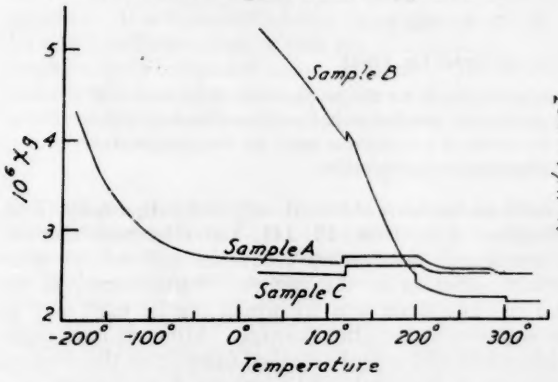
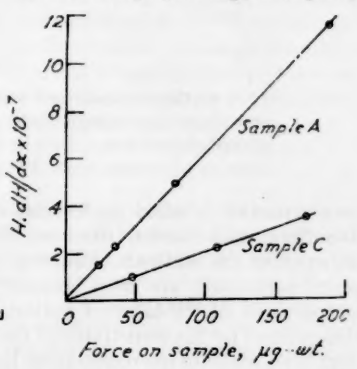


FIG. 2. *Test for ferromagnetic impurity.*



the other methods of investigation. A phase transition at about 475° reported by Ball *et al.* (*loc. cit.*) was not observed in the present investigation since the limit of operation of the balance was about 350°. The lack of results on sample C above 290° was due also to instability which developed in the balance at this point.

Samples A and C were in reasonable agreement in all respects; the slightly higher susceptibility of sample A may be due to the increased impurity, but is not likely to be due to the oxide coating since the susceptibility of plutonium dioxide is very close to that of the metal ($2{\cdot}69 \times 10^{-6}$ per g. at 27°, Dawson, *J.*, 1952, 1882). The susceptibility behaviour of these samples was almost independent of temperature and in this respect was similar to that of uranium (Bates and Hughes, *Proc. Phys. Soc.*, 1954, *B*, **67**, 28). Actually the α-phase showed a slight decrease of susceptibility with increasing temperature which could be predicted on Stoner's free-electron theory ("Magnetism and Matter," Methuen Co., London, 1934, Chap. XIV). Sample B, however, showed a very marked decrease of susceptibility with increasing temperature in both the α- and the β-phase, a type of behaviour found for the lanthanide metals where the susceptibility is due to the presence of ions containing screened unpaired *f*-electrons (*e.g.*, Klemm and Bommer, *Z. anorg. Chem.*, 1937, **231**, 138). The susceptibility at room temperature on a second sample from the same preparation as sample B was $5{\cdot}47 \times 10^{-6}$ per g., also much higher than for samples A and C. It is at present not possible to correlate the different thermomagnetic behaviour with variations of the known impurity contents and it is difficult to attribute it to any preferred orientation

effect. Sample C is believed to represent the nearest approach to the behaviour of pure plutonium metal.

The measurements reported in the tables were obtained by using a maximum field strength of *ca.* 2500 oersteds. It was not possible to extend the measurements to very high field strengths since this would overload the sensitive balance system; in the region 1000—6500 oersteds, however, there was no marked variation of susceptibility with field strength. As an illustration of this, the force acting on the samples in the magnetic field is plotted against $H.\mathrm{d}H/\mathrm{d}x$ in Fig. 2; appreciable amounts of ferromagnetic impurity would be expected to destroy the straight-line relation and to give rise to an intercept on the force axis at $H.\mathrm{d}H/\mathrm{d}x = 0$.

The author thanks members of the Metallurgy Division, A.E.R.E., for supplying the plutonium wire.

ATOMIC ENERGY RESEARCH ESTABLISHMENT,
HARWELL, NR. DIDCOT, BERKS.

[*Received, April 24th*, 1954.]

The Synthesis of Isotopically Labelled Adenosine-2′ Phosphate and Adenosine-3′ Phosphate.

By G. R. BARKER.

[Reprint Order No. 5360.]

A method is described which is suitable for the preparation of adenosine-2′ phosphate and adenosine-3′ phosphate labelled either in the nucleoside or the phosphate residue. Details are given of a technique used for the phosphorylation of adenosine with [^{32}P]phosphorus oxychloride.

ISOTOPICALLY labelled nucleotides have so far been obtained only biosynthetically (Roll, Weinfeld, and Brown, *Biochim. Biophys. Acta*, 1954, **13**, 141, and references therein). Biosynthetical methods, however, necessarily involve low recoveries and, except when micro-organisms are used, considerable dilution of the isotope. Furthermore, in the preparation of ^{32}P-labelled material the maximum activity which can be used may be determined by the sensitivity of the organism to radiation damage. Attempts have therefore been made to overcome these limitations and to find a method suitable for the chemical synthesis of isotopically labelled adenosine-2′ phosphate and adenosine-3′ phosphate.

A synthesis of these nucleotides previously reported (Brown and Todd, *J.*, 1952, 44) involves phosphorylation of 5′-*O*-trityladenosine with dibenzyl phosphochloridate. This method has two disadvantages for the present purpose. First, the use of dibenzyl phosphochloridate necessitates a lengthy preparation of the phosphorylating agent which would be inconvenient with isotopic phosphorus. Secondly, the low yield of 5′-*O*-trityladenosine obtainable by Levene and Tipson's method (*J. Biol. Chem.*, 1937, **121**, 131) make this an unsuitable starting material for the phosphorylation of labelled adenosine. The experiments now reported have been designed to overcome these two difficulties.

In the tritylation of adenosine with 1 mol. of triphenylchloromethane, some $N^6 : O^{5'}$-ditrityladenosine is formed. This fact, besides resulting in a reduced yield of monotrityl compound, means that some adenosine remains unchanged and it would be undesirable to attempt phosphorylation without isolation of the trityladenosine. Tritylation of adenosine with 2 mol. of reagent gave a considerable quantity of the monotrityl compound as well as the dityrityl compound. It is clear that in these circumstances, some triphenylchloromethane is left unchanged and it was therefore unlikely that any adenosine would remain. This assumption is probably correct since no adenosine-5′ phosphate was obtained by phosphorylating the crude mixture of tritylated products.

It was decided to use the commercially available [^{32}P]phosphorus oxychloride for phosphorylation. Earlier attempts (Jachimowicz, *Biochem. Z.*, 1937, **292**, 356; Gulland and Barker, *J.*, 1942, 231) to use this reagent for the phosphorylation of unprotected

adenosine resulted in very poor yields, probably owing partly to the inadequacy of the methods then available for isolation of the products. Furthermore, greater success with this reagent has been achieved more recently (Forrest and Todd, *J.*, 1950, 3295) by carrying out the reaction in the presence of water. The mode of attack of this reagent on adenosine will be discussed in a future communication. Experiment showed that this method could be used successfully for the phosphorylation both of N^6 : $O^{5'}$-ditrityladenosine and of the crude mixture obtained in the tritylation of adenosine. The initial product was obtained by precipitation with water and, after removal of trityl groups with 80% acetic acid, ion-exchange chromatography yielded fractions containing adenosine, adenosine-2′ phosphate, and adenosine-3′ phosphate. The two nucleotides were obtained in an overall yield of 40% from adenosine. Brown and Todd (*loc. cit.*) report a yield of 49% from 5′-*O*-trityl-adenosine which is prepared in 50% yield from adenosine (Levene and Tipson, *loc. cit.*). It is clear, therefore, that the method now described is suitable for the phosphorylation of isotopically labelled adenosine. The method also has the advantage that unchanged adenosine is readily recovered.

On the basis of the phosphorus oxychloride used, approximately 18% of the phosphorus was recovered as total nucleotides. Brown and Todd's results (*loc. cit.*) show a recovery as nucleotides of approximately 10% of the phosphorus of phosphorus trichloride, a 57% yield of the phosphorylating agent (Atherton, Openshaw, and Todd, *J.*, 1945, 382) being assumed. It is thus evident that the method is suitable for preparation of [^{32}P]nucleotides. An additional advantage is that the operations up to the stage of ion-exchange chromatography can be completed within 24 hours. The success of the phosphorylation, however, depends on the purity of the phosphorus oxychloride and a technique for its purification is described which has been used successfully with radioactive material.

Experimental

Tritylation of Adenosine.—To a hot solution of adenosine (1·03 g.) in dry pyridine (30 c.c.) triphenylchloromethane (2·14 g.) was added. The solution was kept for 3 hr. at 95—100° with exclusion of moisture and was then cooled to 0°. In subsequent experiments, this solution (*A*) was treated directly with phosphorus oxychloride. For the isolation of 5′-*O*-trityl- and N^6 : $O^{5'}$-ditrityl-adenosine, the solution was poured into water (400 c.c.) at 0° with vigorous stirring, and the precipitate was collected by filtration, washed with water until free from pyridine, and dried at room temperature. The material (3 g.) was heated on the steam-bath with benzene (50 c.c.) for 45 min. and the 5-*O*-trityladenosine remaining undissolved was collected by filtration of the hot solution, washed with a little benzene, and dried (yield, 0·75 g.). It had m. p. 260° with sintering from 254°. The combined filtrate and washings were concentrated under reduced pressure to 10 c.c. and seeded with N^6 : $O^{5'}$-ditrityladenosine. The product (0·88 g.), after being collected by filtration and dried, had m. p. 200—202°.

Phosphorylation Procedure.—Solution *A* (above) or the corresponding quantity of N^6 : $O^{5'}$-ditrityladenosine in pyridine, was allowed to cool to room temperature and a solution in dry pyridine (5 c.c.) of phosphorus oxychloride (0·75 c.c.) (distilled twice immediately before use, see below) followed by pyridine (2 c.c.) containing water (0·075 c.c.) was added dropwise with stirring. The solution was set aside overnight at room temperature and then cooled to 0° ; 50% aqueous pyridine (10 c.c.) at 0° was added with stirring and the solution was poured into water (400 c.c.). Saturated aqueous barium chloride was added dropwise to coagulate the precipitate which was collected by centrifuging and washed twice with water. The precipitate was boiled under reflux with 80% aqueous acetic acid (70 c.c.) for ½ hr., and the resulting solution was cooled, filtered, and poured into stirred water (500 c.c.). The precipitated triphenylmethanol was filtered off on charcoal and the pH of the filtrate (*B*, see below) brought to 7·5 with hot saturated aqueous barium hydroxide. The solution was diluted to 10 l. and percolated through Dowex-1 ion-exchange resin (10 × 4·5 cm.; mesh size 200—400) in the formate form. The column was washed with water until the effluent was free from barium ions and was eluted first with 0·02N-formic acid (1 l.) and then with 0·15N-formic acid. Fractions (100 c.c.) were collected automatically every 15 min. and the optical density at 260 mμ was determined. Fractions containing adenosine-2′ phosphate were united, concentrated below 40° to 100 c.c., and freeze-dried. The product (0·203 g.) had m. p. 187° (decomp.) and gave one spot (R_P 0·74) on a paper chromatogram developed with a mixture of 5% aqueous disodium hydrogen phosphate

and *iso*amyl alcohol (Carter, *J. Amer. Chem. Soc.*, 1950, **72**, 1466) (Found: C, 34·5; H, 4·5; N, 19·1. Calc. for $C_{10}H_{14}O_7N_5P$: C, 34·6; H, 4·1; N, 20·2%). Fractions containing adenosine-3′ phosphate were combined and the product was isolated in a similar way. The material (0·132 g.) had m. p. 195° (decomp.) and was chromatographically homogeneous, having R_P 0·67 in the same solvent system as above (Found: C, 34·4; H, 4·3; N, 19·0. Calc. for $C_{10}H_{14}O_7N_5P$: C, 34·6; H, 4·1; N, 20·2%).

A portion of the filtrate *B* (above) was adjusted to pH 7·5, diluted to 250 c.c. (optical density of this solution was 0·6 at 260 mμ), and percolated through Dowex-1 ion-exchange resin (30 × 1 cm.) as described above. The column was eluted as previously described and fractions (6 c.c.) were collected every 45 min. The first 64 fractions had zero optical density at 260 mμ; adenosine-2′ phosphate was collected in 16 fractions; a further 47 fractions failed to show absorption and then adenosine-3′ phosphate was collected in 30 fractions. No absorbing material other than these two nucleotides could be detected.

Manipulation of Radioactive Phosphorus Oxychloride.—In using non-radioactive material, distillation of the phosphorus oxychloride at atmospheric pressure in an all-glass apparatus was found to be satisfactory, providing that the first fraction which contains dissolved hydrogen chloride was rejected. Radioactive material was distilled as follows, in the vacuum-apparatus shown in Fig. 1. Silicone grease was used for all taps and joints; trap *A* was cooled in liquid

FIG. 1.

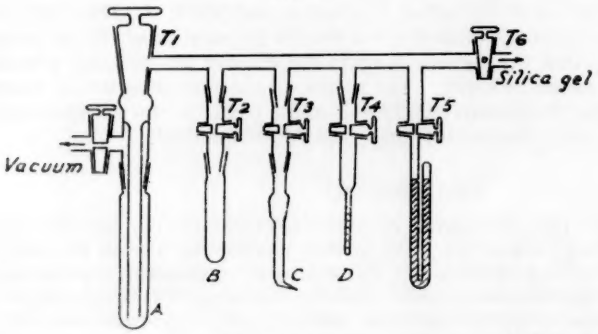


FIG. 2.

nitrogen. An ampoule containing [^{32}P]phosphorus oxychloride (approx. 1 c.c.) was broken and quickly placed in tube *B*, which was then cooled by acetone–solid carbon dioxide and, with taps T_1, T_2, and T_5 open and T_3, T_4, and T_6 closed, the system was evacuated. Tap T_2 was closed, *B* was allowed to attain room temperature, the cooling mixture was replaced, and T_2 was again opened. This process was repeated twice. T_1 and T_5 were then closed, T_4 was opened, the graduated tube *D* was cooled in liquid nitrogen and the cooling mixture was removed from *B*. Periodically, T_4 was closed and the phosphorus oxychloride in *D* was thawed until the required volume had been distilled; T_2 and T_4 were then closed. Pyridine (5 c.c.) was placed in *C* which was cooled in liquid nitrogen and evacuated by opening T_1 and T_3. T_1 was again closed, T_4 was opened, and the phosphorus oxychloride was allowed to distil into *C*. T_3 was then closed and after *C* had reached room temperature, condensed moisture was removed from the outside of the tube. The apparatus shown in Fig. 2 was then attached to *C* by means of joint *J*. Flask *E* contained solution *A* (above) and *F* contained pyridine (2 c.c.) containing the appropriate quantity of water. T_3 and T_6 were opened and, by rotating the apparatus about joint *J*, the capillary at the end of *C* was broken and the contents of *E* were stirred magnetically as the pyridine and phosphorus oxychloride were allowed to enter *E*. When this was complete, *F* was rotated into the position shown by the dotted line. Stirring was continued for a further 5 min., T_3 was closed, and the apparatus left overnight. For subsequent processes, flask *E* was removed and normal techniques were used, with the usual precautions.

Part of this work was carried out during the tenure of a Fellowship of the Rockefeller Foundation, which the author gratefully acknowledges. He also thanks Dr. G. B. Brown for his generous hospitality and facilities provided during the initial stages of the work.

SLOANE KETTERING INSTITUTE FOR CANCER RESEARCH, NEW YORK.
THE UNIVERSITY, MANCHESTER.
[*Received, May 5th,* 1954.]

Experiments on the Synthesis of Lysergic Acid. Part I. Derivatives of Indole.

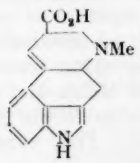
By J. A. Barltrop and D. A. H. Taylor.

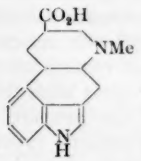
[Reprint Order No. 5368.]

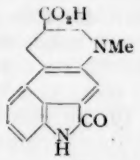
As a model for the synthesis of lysergic acid (I), the compound (VII; R = Me), prepared by condensing 2-methylindole with formyl*cyclo*hexanone, has been reduced to (VI) and cyclised in small yield to the tetracyclic system (VIII) or (IX). A projected alternative, which envisaged the cyclisation of (X) by an intramolecular Grignard reaction, failed because it was found to be impossible to prepare the essential intermediate, 4-bromoindole.

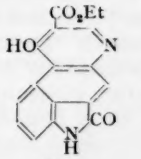
The problem presented by the synthesis of lysergic acid (I) has attracted the attention of several investigators, and two syntheses of dihydrolysergic acid (II) have been reported, the first by Uhle and Jacobs (*J. Org. Chem.*, 1945, **10**, 76), and the second by Stoll and his collaborators (Stoll, Rutschmann, and Schlientz, *Helv. Chim. Acta*, 1950, **33**, 375; Stoll and Rutschmann, *ibid.*, p. 67). So far, however, no synthesis of lysergic acid has been reported. Both syntheses of dihydrolysergic acid, referred to above, produce the trimethyleneindole system peculiar to lysergic acid by the reduction of a naphthastyril. In the first, 8-amino-1 : 2 : 3 : 4-tetrahydro-1-methyl-1-azaphenanthrene-3 : 9-dicarboxylic acid lactam (III) was reduced with sodium in butanol, giving dihydrolysergic acid in small yield, while in the second the reduction of 8-amino-3-ethoxycarbonyl-4-hydroxy-1-azaphenanthrene-9-carboxylic acid lactam (IV) with the same reagent was used to give dihydronorlysergic acid, the methyl ester of which isomerised on heating to give dihydrolysergic acid.

We have been investigating possible methods of synthesising lysergic acid for some time now and, in view of the papers which have recently appeared on this subject, our results may be of interest.

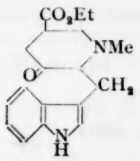

(I)

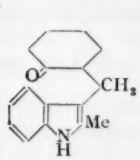

(II)

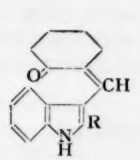

(III)


(IV)

It seems that the crucial point is the introduction of the ethylenic linkage in the 9 : 10-position, and we have thus attempted to design a synthesis in which the double bond appears naturally as an essential feature of the synthesis and does not have to be specially introduced after completion of the ergoline skeleton. We hoped that the cyclisation of 3-(5-ethoxycarbonyl-3-oxo-1-methyl-2-piperidylmethyl)indole (V) might represent such a synthesis, and the present paper records our attempts to perform a model of this scheme.


(V)

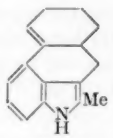

(VI)


(VII)

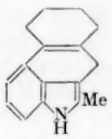
In the first instance, we decided to attempt the ring closure with 2-methyl-3-2′-oxo-*cyclo*hexylmethylindole (VI) as a model, the methyl group being introduced into the indole nucleus in order to prevent cyclisation on to that position. The preparation of this compound was achieved by a two-stage reaction which involved, first, the condensation between formyl*cyclo*hexanone and 2-methylindole, which gave 2-methyl-3-2′-oxo*cyclo*hexylidene-

methylindole (VII; R = Me), and, secondly, the reduction of this compound to (VI) over palladised charcoal, which proceeded smoothly and in good yield. 3-2′-Oxo*cyclo*hexylidenemethylindole (VII; R = H) was also prepared from indole and formyl*cyclo*hexanone, but it was found that 2-phenylindole was not reactive enough to condense except in the presence of hydrogen chloride, a blue substance, apparently of complex structure, being then obtained. Although the substance (VI) resisted the action of phosphoric oxide in boiling toluene, cyclisation was effected in small yield by hot metaphosphoric acid. The product presumably has the structure (VIII) or (IX).

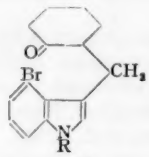
We then attempted to synthesise the substance (X; R = H), a suitably protected derivative of which, it was expected, would cyclise under Grignard conditions. Unfortunately, we have been unable to prepare 4-bromoindole, the required intermediate for the production of (X).



(VIII)



(IX)



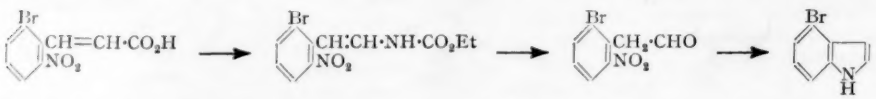
(X)

Uhle (*J. Amer. Chem. Soc.*, 1949, **71**, 761) has prepared 4-chloroindole from 2-chloro-6-nitrotoluene by the Reissert synthesis but, although we were able to obtain 4-bromoindole-2-carboxylic acid by an analogous process, we could not decarboxylate this acid. Similar difficulty in decarboxylating indole acids has been reported by other workers and, indeed, the conditions employed by Uhle for the decarboxylation of 4-chloroindole-2-carboxylic acid, which consisted in refluxing in quinoline with half a molecular proportion of cuprous chloride for 8 hours, seem rather drastic and suggest that this decarboxylation, too, may have proved difficult.

2-Bromo-6-nitrotoluene was readily prepared by brominating *o*-nitrotoluene, following Gluud's method (*Ber.*, 1915, **48**, 433), and fractionally distilling the mixture of isomers obtained. The amounts of 2-bromo-6-nitro- and 4-bromo-2-nitro-toluene obtained were approximately 40% and 50% respectively, the remainder consisting of an unresolved mixture of isomers. This result is in fair agreement with the work of Mehta and Ayyar (*J. Univ. Bombay*, 1942, **10**, 99) who analysed the mixture by oxidation to the bromonitrobenzoic acids, which they separated by fractional crystallisation. They concluded that 40% of the product was 2-bromo-6-nitrotoluene.

The condensation between 2-bromo-6-nitrotoluene and ethyl oxalate in the presence of sodium ethoxide gave 2-bromo-6-nitrophenylpyruvic acid, which was characterised as its semicarbazone. Reduction of 2-bromo-6-nitrophenylpyruvic acid with sodium dithionite (hydrosulphite) or ferrous sulphate and ammonia gave 4-bromoindole-2-carboxylic acid in excellent yield, but this acid could not be decarboxylated under any discoverable conditions. The acid was recovered substantially unchanged after being heated with water at 260° for 3 hours. Refluxing it with quinoline, alone or in the presence of cuprous bromide, cupric oxide, or copper powder, or refluxing it in resorcinol, gave no indoles detectable with Ehrlich's reagent.

6-Bromoindole-2-carboxylic acid was also made from the 4-bromo-2-nitrotoluene



obtained as a by-product in the bromination, and decarboxylation experiments were performed on this less valuable material. These were also not attended with success.

The fusion of 2-bromo-6-formamidotoluene with potassium *tert.*-butoxide, and of the acetyl derivative with sodamide, yielded only negligible amounts of indoles. It is, perhaps, not surprising that the bromine atom should be attacked under these drastic conditions.

An attempt was also made to prepare 4-bromoindole from 2-bromocinnamic acid by the method shown, but the nitration of methyl 2-bromocinnamate gave, not the required methyl 2-bromo-6-nitrocinnamate, but methyl 2-bromo-5-nitrocinnamate. This orientation was established by permanganate oxidation, 2-bromo-5-nitrobenzoic acid being obtained.

Experimental

2-Methyl-3-2′-oxocyclohexylidenemethylindole.—A solution of 2-methylindole (9·5 g.) and 2-formylcyclohexanone (20 g.) in ethanol (50 c.c.) was refluxed for 2 hr. and concentrated under reduced pressure. The viscous residual oil, when taken up in ether and set aside overnight, deposited *2-methyl-3-2′-oxocyclohexylidenemethylindole* (10 g., 57%) in yellow prisms which, after recrystallisation from ethanol, had m. p. 126° (Found: C, 79·6; H, 7·1; N, 6·1. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·1; N, 5·9%). The *dinitrophenylhydrazone* formed orange needles, m. p. 234° (from ethanol) (Found: C, 63·2; H, 4·8. $C_{22}H_{21}O_4N_5$ requires C, 63·0; H, 5·0%).

2-Methyl-3-2′-oxocyclohexylmethylindole.—The above substance (0·67 g.), dissolved in ethanol (50 c.c.), was hydrogenated at room temperature and pressure over palladised charcoal for 1 hr. (absorption 58 c.c.; calc. 63 c.c.). After filtration, the colourless solution was evaporated to dryness *in vacuo*. *2-Methyl-3-2′-oxocyclohexylmethylindole* was obtained as a colourless oil, which slowly reddened in air. For analysis it was regenerated from the recrystallised picrate, by decomposition with ammonia and extraction with ether (Found: C, 79·4; H, 7·9. $C_{16}H_{19}ON$ requires C, 79·7; H, 7·9%). The *picrate* formed very dark red needles, m. p. 135°, from benzene (Found: C, 56·2; H, 4·5. $C_{16}H_{19}ON,C_6H_3O_7N_3$ requires C, 56·2; H, 4·7%). The semicarbazone crystallised from ethanol in colourless plates, m. p. 199—200° (decomp.).

3-2′-Oxocyclohexylidenemethylindole.—A solution of indole (2 g.) and 2-formylcyclohexanone (4 g.) in ethanol (20 c.c.) was refluxed for 2 hr. The solvent having been evaporated under reduced pressure, addition of ether gave a yellow crystalline precipitate. After being kept overnight the solid was collected and recrystallised from ethanol; *3-2′-oxocyclohexylidenemethylindole* was obtained as yellow needles, m. p. 232° (Found: C, 79·75; H, 6·65. $C_{15}H_{15}ON$ requires C, 80·0; H, 6·7%).

Condensation between 2-Phenylindole and 2-Formylcyclohexanone.—A solution of 2-formylcyclohexanone (2 g.) in a little ethanol was added to a solution of 2-phenylindole (1 g.) in ethanol saturated with hydrogen chloride. The deep red liquid was poured into water after 10 min. An intensely blue solid substance was precipitated, which crystallised from ethanol in microscopic crystals, m. p. *ca.* 200° (Found: C, 80·5; H, 6·15; N, 4·3%).

Experiments on the Cyclisation of 2-Methyl-3-2′-oxocyclohexylmethylindole.—(*a*) Phosphoric oxide (4 g.) and syrupy phosphoric acid (3 c.c.) were mixed in a small flask. The temperature rose to 150°. When the temperature had fallen to 130°, 2-methyl-3-2′-oxocyclohexylmethylindole (1 g.) was added, and the mixture stirred in an oil-bath kept at 130° for 2 min. The use of a higher temperature or longer period of heating led to extensive decomposition, and the production of a purple solid. After cooling, water was added, the insoluble residue collected, washed with water, and dissolved in methanol (20 c.c.). The solution was brought to pH 6 by the addition of acetic acid and ammonia, Girard's reagent "P" (2 g.) was added, and the solution was boiled under reflux for 20 min. After dilution with water (200 c.c.) the mixture was adjusted to pH 6·5 with sodium carbonate, and the non-ketonic fraction was extracted with ether. After evaporation of the ether, the residue was converted into its picrate from which, after repeated crystallisation from ethanol, the *picrate* of 4 : 6 : 6*a* : 7 : 8 : 9- (VIII) or 4 : 6 : 7 : 8 : 9 : 10-hexahydro-5-methyldibenz[*cd*, *f*]*iso*indole (IX) (cf. Ring Index No. 2457) was obtained as dark red needles, m. p. 144° (Found: C, 58·8; H, 4·45. $C_{16}H_{17}N,C_6H_3O_7N_3$ requires C, 58·4; H, 4·4%).

(*b*) The ketone (9·3 g.), dissolved in dry toluene (50 c.c.), was refluxed with phosphoric oxide (2 g.) for 1 hr., and the solution was filtered and washed with water. The toluene layer was evaporated and the residue treated with the Girard reagent. No non-ketonic fraction could be isolated.

2-Bromo-6-nitrotoluene.—Crude bromonitrotoluene (1 kg.) obtained as described by Gluud (*loc. cit.*) was fractionated at 15 mm. through a 1-m. column packed with Fenske helices. Three arbitrary fractions (approx. 400, 200, and 400 g.) were collected, of which the first and last largely crystallised. The crystals were collected and the mother-liquors added to the middle fraction, which was again separated into three fractions. The crystals obtained from the two low-boiling fractions were mixed and recrystallized from light petroleum; pure 2-bromo-6-

nitrotoluene (*ca.* 400 g.), m. p. 42°, was obtained (lit., m. p. 42°). From the two higher-boiling fractions there was obtained after recrystallisation 4-bromo-2-nitrotoluene (*ca.* 500 g.), m. p. 47° (lit., m. p. 47°). The mother-liquors were added to the next batch for fractionation. This method of working required practically no attention, and was found to be much more convenient than attempting to cut the fractions accurately.

2-Bromo-6-nitrophenylpyruvic Acid.—A solution of sodium ethoxide, prepared from sodium (23 g.) and ethanol (500 c.c.), was treated with ethyl oxalate (143 g.) and 2-bromo-6-nitrotoluene (216 g.), and the mixture refluxed on the water bath for 45 min. and cooled. Water (500 c.c.) was added and all volatile material was removed by steam-distillation. The residual solution was cooled again, washed with ether, and acidified with hydrochloric acid. A red oil separated which was isolated with ether. *2-Bromo-6-nitrophenylpyruvic acid* was obtained as a red oil (119 g., 41%) which crystallised during 3 months. After recrystallisation from benzene it formed colourless crystals, m. p. 117° (Found: C, 37·8; H, 2·3; Br, 26·7. $C_9H_6O_5NBr$ requires C, 37·5; H, 2·1; Br, 27·8%). From the steam-distillate 2-bromo-6-nitrotoluene (115 g., 53%) was recovered. The *semicarbazone* of 2-bromo-6-nitrophenylpyruvic acid formed colourless crystals, m. p. 216°, from ethanol (Found: C, 35·0; H, 2·45. $C_{10}H_9O_5N_4Br$ requires C, 34·8; H, 2·6%).

4-Bromo-2-nitrophenylpyruvic Acid.—This was prepared by a method analogous to that employed for its isomer. *4-Bromo-2-nitrophenylpyruvic* acid (40%) formed colourless needles, m. p. 144°, from benzene (Found: C, 37·75; H, 2·0; N, 4·75. $C_9H_6O_5NBr$ requires C, 37·5; H, 2·1; N, 4·9%). The recovery of 4-bromo-2-nitrotoluene amounted to 51%.

4-Bromoindole-2-carboxylic Acid.—(*a*) 2-Bromo-6-nitrophenylpyruvic acid (28 g.) was reduced with a boiling solution of ferrous sulphate heptahydrate (150 g.) and ammonia (60 c.c.; *d* 0·880) in water (600 c.c.) for 5 min., and filtered hot. The precipitate, on repeated extraction with boiling dilute ammonia and acidification, gave *4-bromoindole-2-carboxylic acid* (18 g., 75%), fluffy needles, m. p. 266° (from ethanol) (Found: C, 45·0; H, 2·7; N, 6·4. $C_9H_6O_2NBr$ requires C, 45·0; H, 2·5; N, 5·8%).

(*b*) 2-Bromo-6-nitrophenylpyruvic acid (28 g.) was dissolved in 10% sodium hydroxide solution (45 c.c.), and water (100 c.c.) added. The deep red solution thus obtained was cooled in ice and stirred mechanically while sodium dithionite (53 g.) was added during 1 hr. The solution was acidified with hydrochloric acid, heated on a steam-bath for 2 hr. to expel sulphur dioxide, and then cooled. The acid (22 g., 90%) was collected and crystallised from aqueous ethanol.

6-Bromoindole-2-carboxylic Acid.—This was prepared by the same methods as was its isomer. The *acid* formed colourless needles, m. p. 223°, from aqueous ethanol (Found: C, 44·8; H, 2·6; N, 6·3%).

2-Bromo-6-formamidotoluene.—2-Bromo-6-nitrotoluene (21·6 g.), suspended in ethanol (50 c.c.), was hydrogenated over Raney nickel at room temperature and an initial pressure of 3 atm. As the reduction proceeded the nitro-compound passed into solution. After complete reduction the solution was filtered from catalyst and evaporated. 2-Amino-6-bromotoluene (17 g., 92%) distilled as a colourless oil at 130°/16 mm. The amine (9·3 g.) in anhydrous formic acid (20 c.c.) was kept on the steam-bath overnight. In the morning, the solution was diluted with water, and the product collected, and crystallised from benzene. *2-Bromo-6-formamidotoluene* (10 g., 93%) formed leaflets, m. p. 116° (Found: C, 44·6; H, 4·0; Br, 36·5. C_8H_8ONBr requires C, 44·9; H, 3·7; Br, 37·4%).

4-Bromo-2-formamidotoluene, prepared similarly, separated from benzene in colourless needles, m. p. 137° (Found: C, 45·0; H, 4·0; Br, 36·6%).

Attempted Preparation of 4-Bromoindole.—Potassium (2·9 g.) was dissolved in *tert.*-butanol (100 c.c.), and 2-bromo-6-formamidotoluene (16 g.) was added. The butanol was distilled in a current of nitrogen, and the residue heated to 270° for 0·5 hr. and allowed to cool under nitrogen. The residue was treated with water and extracted with ether. The ethereal extract gave no colour with Ehrlich's reagent. Repetition of the experiment at various temperatures gave no more favourable results.

Attempted Preparation of 4-Bromo-2-methylindole.—2-Acetamido-6-bromotoluene (34 g.) was finely powdered and mixed with sodamide (14 g.) similarly powdered. The mixture was covered with dry ether, ammonia being at once evolved. The mixture was warmed gently under a current of dry nitrogen, until the evolution of ammonia ceased, and then heated in a metal-bath at 240° for 15 min. The mixture was cooled, and treated with aqueous ethanol (50 c.c. of 50%). After being warmed on the steam-bath for a short time, the solution was diluted with water and extracted with ether. The ethereal extract was washed with dilute acid and then with sodium

hydrogen carbonate solution, dried, and evaporated. A small amount of oil remained which gave a fairly strong Ehrlich test but did not suffice for purification.

Methyl 2-Bromo-5-nitrocinnamate.—Methyl 2-bromocinnamate (11·4 g.) was dissolved at 0° in concentrated sulphuric acid. A solution of nitric acid (3·5 c.c.; *d* 1·48) in sulphuric acid (10 c.c.) was added during 0·5 hr. with mechanical stirring and cooling. The mixture was then poured on cracked ice, and the precipitate collected, washed with much water, and dried. The solid (13·7 g.) thus obtained was boiled with successive small amounts of methanol, in which it was rather insoluble, to remove more soluble impurities. After three washings in this way, the residue had m. p. 166°. After crystallization from a large volume of methanol, *methyl 2-bromo-5-nitrocinnamate* formed very pale yellow needles (9·5 g., 70%), m. p. 169° (Found: C, 42·1; H, 2·8. $C_{10}H_8O_4NBr$ requires C, 42·0; H, 2·8%).

2-Bromo-5-nitrobenzoic Acid.—Methyl 2-bromo-5-nitrocinnamate (6 g.), suspended in 50% sulphuric acid (50 c.c.), was treated with a saturated solution of potassium permanganate (7 g.). The solution was boiled for a few minutes, and then filtered hot. On cooling, 2-bromo-5-nitrobenzoic acid (2·4 g.) separated in long, colourless needles. After recrystallisation from aqueous ethanol, it had m. p. 178° alone and when mixed with an authentic specimen.

One of us (D. A. H. T.) thanks the Department of Scientific and Industrial Research for a maintenance allowance.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, May 5th,* 1954.]

Experiments on the Synthesis of Lysergic Acid. Part II. Derivatives of 1-Azaphenanthrene.*

By J. A. BARLTROP and D. A. H. TAYLOR

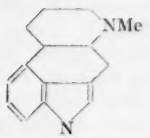
[Reprint Order No. 5369.]

3 : 4-Trimethyleneindole (I) has been prepared by cyclising *N*-formyl-5 : 6 : 7 : 8-tetrahydro-1-naphthylamine. A number of substituted and reduced 1-azaphenanthrenes have been prepared as intermediates for the synthesis of the ergoline ring system.

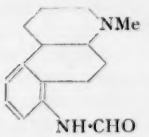
THIS paper is largely concerned with an investigation of derivatives of 1-azaphenanthrene which are related to lysergic acid and from which the ergoline system might be obtained by finally fabricating the pyrrole ring.

Initial experiments established that 3 : 4-trimethyleneindole (1 : 3 : 4 : 5-tetrahydrobenz[*cd*]indole) (I) could be prepared in 5% yield by fusing *N*-formyl-5 : 6 : 7 : 8-tetrahydro-1-naphthylamine with potassium *tert.*-butoxide. An extension of this mode of synthesis to 6-methylergoline (II) would require 8-formamido-1-methyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-1-azaphenanthrene (III) as an intermediate. This we attempted to prepare

(I)



(II)



(III)

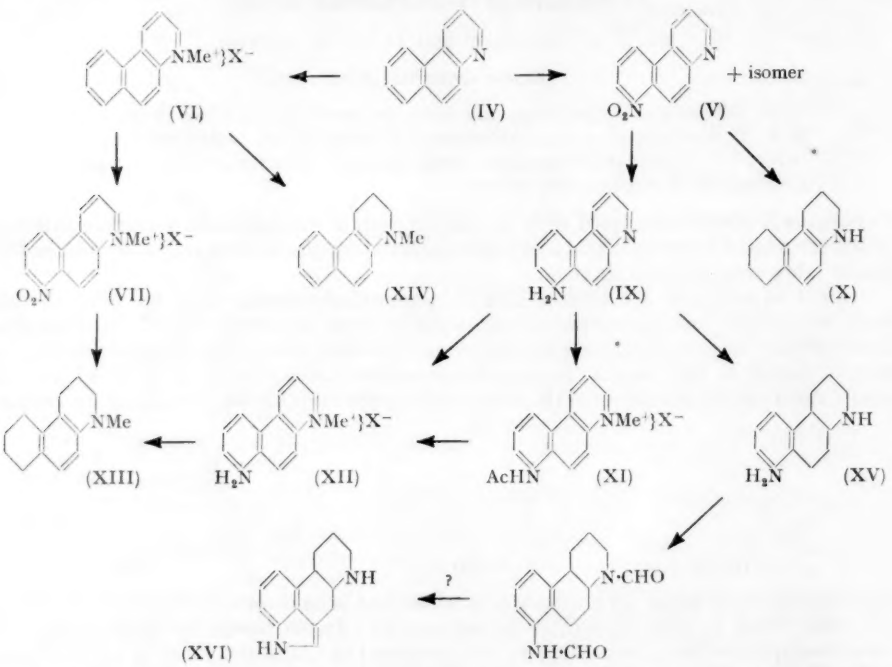
from 1-azaphenanthrene (IV), nitration of which had been shown by Armit and Robinson (*J.*, 1925, 1614) to yield the 8-nitro-derivatives (V). In our hands, the preparation of 8-nitro-1-azaphenanthrene according to the directions of Claus and Besseler (*J. pr. Chem.*, 1898, **57**, 63) and Hepner, (*Monatsh.*, 1906, **27**, 1053) gave only small yields, but under modified conditions an almost quantitative yield of mononitro-derivatives was obtained. From these, we have isolated in addition to the known 8-nitro-compound, a new isomer which has been characterised by reduction to the corresponding amine but not orientated.

Nitration of 1-azaphenanthrene methosulphate (VI; X = $MeSO_4$) proceeded in good

* Part I, preceding paper.

yield, the major product being 8-nitro-1-azaphenanthrene methosulphate (VII; X = $MeSO_4$) which was isolated as the derived picrate and identified as the chloride. The method is not so convenient as that described above. Reduction of 8-nitro-1-azaphenanthrene to the 8-amino-compound (IX) with stannous chloride as described by Claus and Besseler (*loc. cit.*) is very satisfactory and, in our view, considerably more convenient than the method of Armit and Robinson (*loc. cit.*) who used sodium sulphide in boiling aniline. Catalytic hydrogenation of the nitro-compound over Raney nickel gave an octahydro-azaphenanthrene, identified through its *N*-nitroso-derivative as the 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-isomer (X), which had been previously prepared by Bamberger and Müller (*Ber.*, 1891, **24**, 2660) by reducing 1-azaphenanthrene with sodium and amyl alcohol. The loss of the nitro-group presumably depends on the intermediate formation of 8-amino-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-1-azaphenanthrene, which as a benzylamine undergoes hydrogenolysis. The direct conversion of the amine (IX) into its methiodide (XII; X = I) as described by Claus and Besseler (*loc. cit.*) was found to give poor yields and a large amount of tar was formed. However, if the primary amino-group was first protected by acetylation, the acetyl methiodide (XI) was readily obtained and hydrolysis then gave the required methochloride (XII; X = Cl).

Hydrogenation of the methochloride over Raney nickel in the presence of diethylamine (cf. Barltrop and Taylor, *J.*, 1951, 108) did not lead to the required product, but proceeded with the elimination of the primary amino-group to give an octahydro-*N*-methylazaphenanthrene which, from analogy with the formation of (X) from (V), is believed to be 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-1-methyl-1-azaphenanthrene (XIII). This substance



was also obtained by the catalytic hydrogenation of 8-nitro-1-azaphenanthrene methochloride (VII; X = Cl). An alternative route to the required intermediate (III) appeared to lie in the nitration of 1-methyl-1 : 2 : 3 : 4-tetrahydro-1-azaphenanthrene (XIV) (Barltrop and Taylor, *loc. cit.*), but only tars were obtained from the reaction.

Success was ultimately attained by reducing 8-amino-1-azaphenanthrene with sodium and amyl alcohol. This gave 8-amino-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-1-azaphen-

anthrene (XV), the structure of which follows from the fact that it could be diazotised and coupled with β-naphthol to give a deep red dye. The diformyl derivative of this compound was fused with potassium *tert.*-butoxide and a product obtained which gave the characteristic Keller test for the ergot alkaloids when treated with Ehrlich's reagent. The colour reaction was presumably due to the presence of a small amount of ergoline (XVI) or of its *N*-formyl derivative, but the amount obtained was too small to permit its isolation.

Experimental

3 : 4-*Trimethyleneindole* (1 : 3 : 4 : 5-*Tetrahydrobenz*[cd]*indole*).—5 : 6 : 7 : 8-Tetrahydro-1-naphthylamine (20 g.) was heated on the steam-bath overnight with anhydrous formic acid (20 c.c.) and distilled. The *formyl* derivative (20·2 g.) was collected at 245°/44 mm. A specimen, recrystallised from benzene, formed colourless crystals, m. p. 98° (Found: C, 75·5; H, 7·6. $C_{11}H_{13}ON$ requires C, 75·4; H, 7·4%). Potassium (6·6 g.) was dissolved in *tert.*-butanol (140 c.c.), and the *N*-formyltetrahydronaphthylamine (20 g.) was added. The solvent was evaporated in nitrogen, and the residue heated at 240° during 1 hr. and finally to 300° with a slow stream of nitrogen continually passing. When cold, water was added and, the soluble products were isolated with chloroform, then dissolved in low-boiling petroleum and adsorbed on an alumina column. The chromatogram was developed with benzene containing 5% of chloroform. The first fraction of eluate yielded, on evaporation, a pale brown oil which soon crystallised. Sublimation of this material in a high vacuum yielded 3 : 4-trimethyleneindole (1 g.) as colourless plates, m. p. 53°. Recrystallisation from petroleum raised the m. p. to 56° (Found: C, 84·0; H, 7·1. Calc. for $C_{11}H_{11}N$: C, 84·1; H, 7·0%). Jacobs and Craig (*J. Biol. Chem.*, 1934, **106**, 393) give m. p. 56°. The picrate, prepared in ethanol, had m. p. 165° (Jacobs and Craig, *loc. cit.*, give m. p. 165°). The substance gave a colour reaction with Erlich's reagent very similar to that given by skatole.

Nitration of **1-*Azaphenanthrene*.**—After a systematic investigation, the following procedure was found to give the best results. Finely powdered 1-azaphenanthrene (89·5 g.) was added with stirring to fuming nitric acid (360 c.c.) cooled in ice, and kept overnight in a refrigerator. The mixture was poured into water preheated to 90°, cautiously neutralised with ammonia, and allowed to cool. The product (100—110 g.) was collected, dried, and extracted with benzene (2 × 200 c.c.). The undissolved residue, crystallised from ethanol, gave 8-nitro-1-azaphenanthrene (85 g.), m. p. 165°. Claus and Besseler (*loc. cit.*) give m. p. 165°. Occasionally, crystals of m. p. 173° were obtained instead. These appear to be a polymorphic form since, on reduction, both forms give the same amine. This m. p. is also recorded, without comment, by Hepner.

The benzene extract was purified by filtering through a 1 cm. layer of alumina and concentrated. A product of m. p. *ca.* 100° separated. It was purified by chromatography in benzene on alumina. The first fraction of eluate deposited stout yellow prisms of x-*nitro*-1-*azaphenanthrene*, m. p. 145° (Found: C, 69·6; H, 3·8. $C_{13}H_8O_2N_2$ requires C, 69·65; H, 3·6%).

Nitration of **1-*Azaphenanthrene Methosulphate*.**—1-Azaphenanthrene (9 g.) and methyl sulphate (6 g.) were heated together on the steam-bath for 10 min. After crystallisation from methanol, 1-*azaphenanthrene methosulphate* formed needles, m. p. 177° (Found: C, 59·2; H, 4·8. $C_{15}H_{15}O_4NS$ requires C, 59·0; H, 4·9%). The material so obtained was dissolved in concentrated sulphuric acid (10 c.c.) and cooled in ice. A mixture of fuming nitric acid (2 c.c.) and sulphuric acid (5 c.c.) was added with stirring during 10 min., the temperature being kept at 0°. After 30 min. the mixture was poured on ice (400 g.), allowed to attain room temperature, then treated with an aqueous solution of picric acid (15 g.). The precipitate was collected, and washed with ethanol to remove excess of picric acid, giving crude 8-*nitro*-1-*azaphenanthrene methopicrate* (17 g., 93%). A specimen, crystallised from ethanol, formed yellow needles, m. p. 253° (Found: C, 51·1; H, 2·5. $C_{20}H_{14}O_9N_5$ requires C, 51·3; H, 3·0%). The picrate (10 g.), suspended in concentrated hydrochloric acid (100 c.c.), was washed with benzene until all picric acid had been extracted. The aqueous layer was evaporated and the methochloride crystallised several times from ethanol. It formed fawn-coloured prisms, m. p. 216° (Found: C, 61·1; H, 3·9. Calc. for $C_{14}H_{11}O_2N_2Cl$: C, 61·3; H, 4·0%). Claus and Besseler (*loc. cit.*) give m. p. 218°.

Reduction of **8-*Nitro*-1-*azaphenanthrene*.**—(*a*) By following the directions of Claus and Besseler, 8-amino-1-azaphenanthrene was obtained in 73% yield (m. p. 158°).

(*b*) 8-Nitro-1-azaphenanthrene (17·5 g.), dissolved in ethanol (100 c.c.), was hydrogenated over Raney nickel at 90° for 2 hr. The solution, which had a strong odour of ammonia, was filtered

and evaporated and the residual oil, dissolved in benzene–light petroleum, was chromatographed on alumina. The only pure substance isolatable was 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-1-azaphenanthreme, the *N*-nitroso-derivative of which had m. p. 106°, alone and when mixed with an authentic specimen (Bamberger and Müller, *Ber.*, 1891, **24**, 2660).

x-*Amino*-1-*azaphenanthrene*.—Reduction of *x*-nitro-1-azaphenanthrene with stannous chloride in concentrated hydrochloric acid at 100° gave x-*amino*-1-*azaphenanthrene* as yellow needles, m. p. 175° (Found : C, 80·5; H, 5·0. $C_{13}H_{10}N_2$ requires C, 80·4; H, 5·15%). This compound does not form a brilliant scarlet monoacid cation similar to that which is so characteristic of its isomer.

8-*Acetamido*-1-*azaphenanthrene Methiodide*.—8-Amino-1-azaphenanthrene (15 g.) was boiled for a short time with acetic acid (50 c.c.) and acetic anhydride (15 c.c.). The solution, after being poured into water and made alkaline with ammonia, deposited 8-*acetamido*-1-*azaphenanthrene*, which crystallised from aqueous ethanol in colourless needles, m. p. 227° (Found : C, 70·7; H, 5·7. $C_{15}H_{12}ON_2,H_2O$ requires C, 70·9; H, 5·5%). The acetyl derivative (6 g.) was heated for 1 hr. at 100° with methyl iodide (6 c.c.). Crystallisation of the product from aqueous ethanol gave 8-*acetamido*-1-*azaphenanthrene methiodide* (9·2 g.) as fine orange needles, m. p. 282° (Found : C, 49·8; H, 4·3. $C_{16}H_{15}ON_2I,\frac{1}{2}H_2O$ requires C, 49·6; H, 4·4%).

8-*Amino*-1-*azaphenanthrene Methochloride*.—The above methiodide (5 g.) was hydrolysed by boiling it for 10 min. with concentrated hydrochloric acid (20 c.c.). Basification with ammonia gave the methochloride, which crystallised from ethanol in red needles, m. p. 256°. Claus and Besseler (*loc. cit.*) give m. p. 256°.

Reduction of 8-*Amino*-1-*azaphenanthrene Methochloride*.—The above methochloride (5 g.), dissolved in ethanol (100 c.c.) and diethylamine (10 c.c.), was hydrogenated over Raney nickel for 3½ hr. at 120° and an initial pressure of hydrogen of 100 atm. The solution, after filtration from catalyst, was evaporated to dryness and the residue taken up in dilute hydrochloric acid and washed with ether. Basification gave an oil, which was isolated with ether and converted into its picrate. Crystallisation from ethanol gave 1-*methyl*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-*octahydro*-1-*azaphenanthrene picrate* as needles, m. p. 173° (Found : C, 55·9; H, 5·1; N, 12·7. $C_{14}H_{19}N,C_6H_3O_7N_3$ requires C, 55·8; H, 5·1; N, 13·0%). Neither 8-amino-1-azaphenanthrene methiodide nor its acetyl derivative could be reduced at room temperature over Adams catalyst.

Reduction of 8-*Nitro*-1-*azaphenanthrene Methochloride*.—8-Nitro-1-azaphenanthrene methochloride (5 g.), suspended in ethanol (90 c.c.) and piperidine (10 c.c.), was hydrogenated over Raney nickel for 3 hr. at 120° with an initial pressure of hydrogen of 100 atm. Distillation, after filtration from catalyst, gave 1-*methyl*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-*octahydro*-1-*azaphenanthrene* (1·6 g.), b. p. 200°/7 mm. (Found : C, 83·8; H, 9·4. $C_{14}H_{19}N$ requires C, 83·6; H, 9·45%). The picrate formed needles, m. p. 173°, alone and when mixed with a specimen prepared as described above.

8-*Amino*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-1-*azaphenanthrene*.—8-Amino-1-azaphenanthrene (5·7 g.), dissolved in boiling amyl alcohol (200 c.c.), was poured on to sodium (10 g.) in a flask fitted with a reflux condenser, and then boiled until all the sodium had dissolved. Water (200 c.c.) was added to the cool solution, and the organic layer was separated, washed with water, and acidified with hydrochloric acid. The amyl alcohol was distilled in steam, and the residual aqueous solution basified. 8-*Amino*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-1-*azaphenanthrene* was isolated with ether and was obtained, after distillation, as a pale yellow oil (4·5 g.) (Found : C, 77·4; H, 9·0. $C_{13}H_{18}N_2$ requires C, 77·2; H, 8·9%). The base gave a hydrochloride crystallising from ethanol–ether in needles, m. p. *ca.* 220° (decomp.) depending on the rate of heating. The hydrochloride, diazotised and coupled with β-naphthol, gave a deep red solution.

The authors thank the Department of Scientific and Industrial Research for a grant to one of them (D. A. H. T.).

Dyson Perrins Laboratory, Oxford University. [*Received, May 5th,* 1954.]

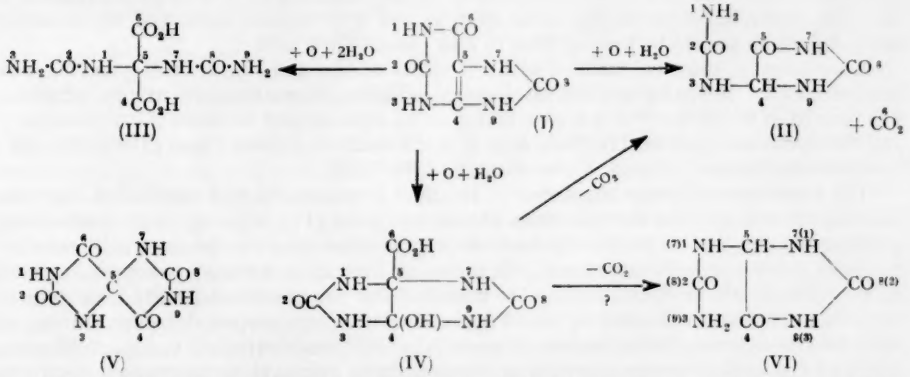
The Mechanism for the Conversions of Uric Acid into Allantoin and Glycine.

By C. E. Dalgliesh and A. Neuberger.

[Reprint Order No. 5372.]

Uric acids labelled with ^{14}C in positions 4, 5, and 6 have been prepared. Oxidation to allantoin with alkaline permanganate, which is probably mechanistically similar to the action of uricase, is accompanied by a rearrangement, the methylene-carbon atom of the hydantoin moiety of allantoin being derived from $C_{(4)}$ of uric acid and the adjacent carbonyl-carbon atom from $C_{(5)}$. On acid hydrolysis of uric acid to glycine, the glycine methylene-carbon atom is derived from $C_{(5)}$ of uric acid and the glycine carboxyl-carbon atom equally from $C_{(4)}$ and $C_{(6)}$. Possible mechanisms for these transformations are suggested.

Quantitatively, the most important product of the oxidation of uric acid (I) under slightly alkaline, neutral, or weakly acidic conditions is allantoin (II) which was first obtained by Liebig and Wöhler (*Annalen*, 1838, **26**, 285) on treatment of uric acid with lead oxide. Many other oxidising agents were later shown to produce allantoin as the main or even the sole product. It was at first thought that this reaction consisted simply of an oxidation of $C_{(5)}$ associated with the removal of $C_{(5)}$ as carbon dioxide, the hydantoin part of allantoin being derived exclusively from the glyoxaline moiety of uric acid. But this simple explanation was found to be untenable.



(In order to facilitate discussion the atoms of the intermediates and products will be numbered according to the carbon and nitrogen atoms of uric acid from which they are thought to be derived.)

Another oxidation product of uric acid, formed in relatively large quantities if the reaction is carried out in strongly alkaline solution, was discovered by Stadeler (*Annalen*, 1867, **78**, 286) and named by him uroxanic acid. The structure of this compound as diureidomalonic acid (III) was established much later by Behrend (*Annalen*, 1904, **333**, 150; see also Behrend and Schultz, *ibid.*, 1909, **365**, 23), but the mechanism of its formation from (I) is not immediately obvious. It appeared almost certain that the malonic acid portion of (III) is derived from $C_{(4)}$, $C_{(5)}$, and $C_{(6)}$ of uric acid and it thus followed that during or after the oxidation of uric acid to uroxanic acid either $N_{(1)}$ or $N_{(3)}$ had become attached to C_5. Evidence was also obtained to suggest that these two oxidation products are not formed by completely independent pathways. Both Behrend (*loc. cit.*) and Sundwik (*Z. physiol. Chem.*, 1904, **41**, 343) reported that, if a solution of uric acid which had been oxidised in a slightly alkaline medium was acidified with acetic acid at the end of the reaction, an almost quantitative yield of allantoin resulted. If, however, more alkali was

added and the solution later acidified with a mineral acid, a large amount of uroxanic acid with little allantoin was obtained. This suggests that both (II) and (III) are derived from a common, labile intermediate.

The formation of a symmetrical intermediate was also suggested by the work of Fischer and Ach (*Ber.*, 1899, **32**, 2731) who found that the oxidation of both 1- and 7-methyluric acid gave the same methylallantoin, *i.e.*, 3-methyl-5-ureidohydantoin, whilst 3- and 9-methyluric acid yielded 1-methyl-5-ureidohydantoin. Fischer and Ach concluded that the glyoxaline ring must have been opened during the oxidation giving as the primary product an open-chain system of unknown structure, but containing the necessary element of symmetry with respect to the two ureido-groups. Behrend (*loc. cit.*) suggested that the primary product was the symmetrical bicyclic acid (IV) which he called "hydroxyacetylene diureide carboxylic acid" and which is systematically named 5-hydroxy-3 : 7-dioxo-2 : 4 : 6 : 8-tetra-aza*bicyclo*[3 : 3 : 0]octane-1-carboxylic acid. This acid might be hydrolysed by attack of a hydroxyl ion on $C_{(4)}$, giving uroxanic acid, or be decarboxylated in an acidic medium with simultaneous opening of one ring to give allantoin. Behrend was unable to isolate (IV) or a derivative thereof, but Schuler and Reindel (*Z. physiol. Chem.*, 1932, **208**, 248) obtained a trisilver salt of (IV), giving a reasonably good analysis, which on treatment with hydrogen sulphide lost carbon dioxide readily to yield allantoin However, this salt was rather unstable and could not be recrystallised. The structure (IV) for this intermediate is based on inference and exclusion of other possibilities. Uroxanic acid itself cannot be the primary product since it is much less easily decarboxylated in acid than the immediate product of the oxidation and gives allantoin in rather poor yield. Moreover, if (III) were an intermediate in the formation of (II), 1- and 7-methyluric acid should give a derivative of 1-methylhydantoin, and 3- and 9-methyluric acid should yield the ureido-compound of 3-methylhydantoin. If *spiro*hydantoin (V) were an intermediate, the same methylallantoin should arise from 1- and 9-methyluric acid, and the isomeric methylallantoin should be formed from 3- and 7-methyluric acid.

More recently, uric acid labelled with ^{15}N either on $N_{(1)}$ and $N_{(3)}$, or on $N_{(7)}$ and $N_{(9)}$ has been prepared. It was found that, on chemical oxidation or reaction with uricase, allantoin was formed in which the ^{15}N was distributed to an equal extent between the ureido-group and the hydantoin part of (II) (Brown, Roll, and Cavalieri, *J. Biol. Chem.*, 1947, **171**, 835; Cavalieri and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 1242).

The reaction mechanism suggested by Behrend is reasonably well established, but certain doubts remain. In the first place the intermediate (IV) is poorly characterised and attempts on our part to prepare derivatives or salts other than the trisilver salt, referred to above, have been without success. It is also, at first sight, not easy to see why an acid such as (IV) should be decarboxylated so readily. But the greatest difficulty is the following: The simplest mechanism by which one of the two rings is opened, before, during, or after decarboxylation, is the rupture of one of the C–N bonds attached to $C_{(4)}$, yielding an allantoin the carbon atoms of which are derived from uric acid in the manner shown in formula (VI). Such a hydrolysis would be analogous to the reaction leading to uroxanic acid. However, the results with the *N*-methyluric acids show that, at least with these compounds, this formulation cannot be correct and it is likely, therefore, that the simple mechanism discussed does not apply to uric acid either. Fischer and Ach's results strongly suggest that the origins of the carbon atoms in allantoin are represented by (II), but it was felt that further, more direct evidence, such as can be provided by isotope experiments, was desirable before an attempt was made to explain the mechanism of the reaction. A better understanding of the detailed mechanism by which uric acid is converted into allantoin is not only of intrinsic chemical interest, but is also of biochemical importance. It appears highly probable (for review, see Bentley and Neuberger, *Biochem. J.*, 1952, **52**, 694) that the mechanisms of oxidation of uric acid by uricase and by permanganate are almost identical; in particular it has been shown that the primary product of enzymic oxidation has the same number of carbon atoms as uric acid. Schuler and Reindel (*Z. physiol. Chem.*, 1933, **215**, 258), moreover, succeeded in isolating, after oxidation of uric acid by uricase, a trisilver salt apparently identical with that obtained after chemical oxidation. In addition, the oxidation of uric acid by chemical means at an alkaline pH has been used

to identify the biogenetic source of each carbon atom of purines (Buchanan, Sonn, and Delluva, *J. Biol. Chem.*, 1948, **173**, 81).

Samples of uric acid which were labelled with ^{14}C at positions 4, 5, and 6 severally were therefore prepared. The methods were essentially those employed in an earlier investigation (Bentley and Neuberger, *loc. cit.*), but with certain modifications giving improved yields. The three labelled uric acids were then converted into allantoin and hydantoin by standard methods. The hydantoin was hydrolysed with alkali to yield glycine which was isolated as its *N*-benzoyl derivative. The hippuric acid was hydrolysed and the free glycine was oxidised with ninhydrin to yield formaldehyde and carbon dioxide; these are known to be derived from the methylene and the carboxyl group of glycine respectively.

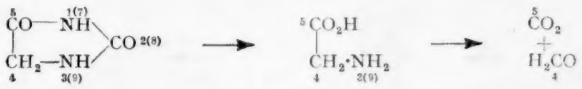


Table 1 shows clearly that $C_{(6)}$ of uric acid is completely lost on conversion of the latter into allantion; this confirms earlier results (Bentley and Neuberger, *loc. cit.*) which showed that the carbon dioxide produced on oxidation of [6-^{14}C]uric acid with uricase had a high

TABLE 1. *Activities of allantoin and hydantoin derived from uric acid.*

(Expressed as counts per carbon atom at infinite thickness on 1 sq. cm. discs; dilutions with non-isotopic material are allowed for in the calculated values.)

Expt.	Starting material and its activity		Activity of allantoin: obs.	Activity of allantoin: calc.*	Activity of hydantoin: obs.	Activity of hydantoin: calc.*
1	[4-^{14}C]Uric acid	2230	2640	2780	1780	1730
2	,,	2230	2680	2780	3570	3450
3	[5-^{14}C]Uric acid	840	1010	1050	700	670
4	,,	840	1010	1050	1400	1350
5	[6-^{14}C]Uric acid	370	0	0	—	—
6	,,	370	0	0	—	—

* Calc. by assuming that $C_{(6)}$ of the initial uric acid is lost.

radioactivity. It can be deduced from Table 2 that the methylene group of glycine is derived from $C_{(4)}$ of uric acid and the carboxyl group from $C_{(5)}$. It thus follows, in agreement with Fischer and Ach's results (*loc. cit.*) with methyluric acids, that the derivation of the carbon atoms in allantoin from those of uric acid is correctly presented by formula (II).

Probable Mechanism of the Conversion of Uric Acid into Allantoin.—In earlier experiments (Bentley and Neuberger, *loc. cit.*) the oxidation of uric acid by uricase was studied by using water and gaseous oxygen labelled with ^{18}O. The conclusion was reached that the enzyme catalyses the transfer of two electrons from the urate ion to oxygen, yielding as the first product the bicyclic acid (IV). A similar mechanism is now suggested for the oxidation by chemical agents in an alkaline medium: the urate ion which may be represented by the formula (VII) or (VIII) loses two electrons and is thus converted into the

TABLE 2. *Degradation of glycine derived from uric acid by way of allantoin and hydantoin.**

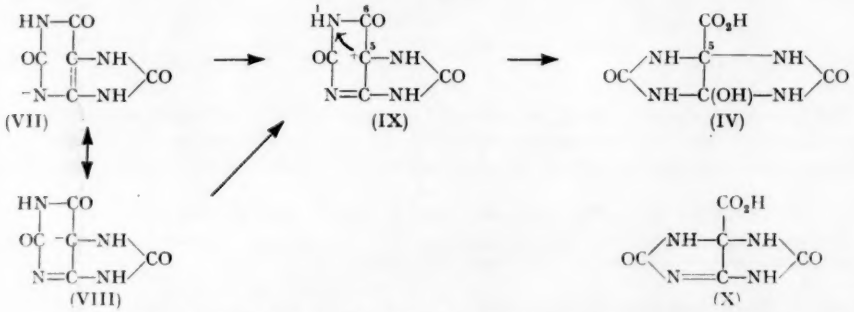
Expt.	Starting material	Calc. activity of glycine based on observed activity of hydantoin	Activity of formaldehyde–dimedone derived from glycine $-CH_2-$: obs.	Activity of formaldehyde–dimedone derived from glycine $-CH_2-$: calc.†	Activity of $BaCO_3$ derived from glycine $-CO_2H$: obs.	Activity of $BaCO_3$ derived from glycine $-CO_2H$: calc.†
1	[4-^{14}C]Uric acid	2590	4280	5180	0	0
2	,,	5180	8520	10360	0	0
3	[5-^{14}C]Uric acid	1000	0	0	1890	2000
4	,,	2030	0	0	4000	4060

* Activities expressed as in Table 1.

† Values calculated assuming C_5 of initial uric acid becomes the glycine carboxyl carbon atom and C_4 the glycine α-carbon atom.

carbonium ion (IX). Interaction of the strongly electrophilic 5-carbon atom with the 1-nitrogen atom, followed by the rupture of the bond joining $N_{(1)}$ to $C_{(6)}$ and loss of proton will give (X). This structure (X) was originally suggested by Bentley and Neuberger for

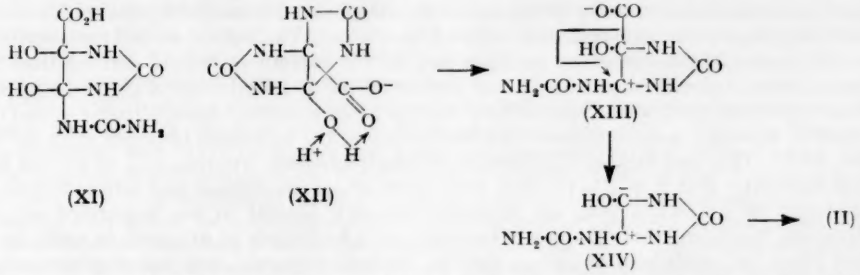
the bicyclic acid isolated by Reindel and Schuler (*loc. cit.*). However, such a structure appears unlikely since it contains a double bond at the bridgehead of two five-membered rings. It is now recognised (for references, see Fawcett, *Chem. Reviews*, 1950, **47**, 219) that Bredt's rule applies to carbon–nitrogen bonds as well as to carbon–carbon bonds. The " glycoluril " system is almost certainly, unlike that of uric acid, non-aromatic and the presence of a double bond in the position indicated by (IX) would involve a great distortion of bond angles and thus raise the energy of the molecule. It is therefore suggested that concomitant with the rearrangement proposed above, there is addition of water to the double bond leading to the acid (IV).



The conversion of the acid (IV) into allantoin involves opening of one of the two rings, decarboxylation, and a shift of the oxygen from position (4) to position (5). The last-mentioned step is most likely to be a pinacol type of rearrangement, as already suggested by Biltz and Max (*Ber.*, 1921, **54**, 2451). The order in which the various changes take place is uncertain, but it is possible that the first step is hydrolysis of the bond $N_{(1)}$–$C_{(5)}$, giving the dihydroxy-acid (XI). A more reasonable mechanism however, involves as the initial step an electrophilic attack of a proton on the β-hydroxy-group of the anion of (IV), giving a transitory intermediate of carbonium ion-type. However, the steric requirements of the tervalent carbon atom will impose a considerable steric strain on the bicyclic system and it is therefore suggested, that the ionisation of the β-carbon atom is associated with the opening of one of the two rings. The attack of the proton is probably facilitated by the existence of a hydrogen bond between the carbonyl-oxygen atom of the carboxylate group and the hydrogen atom of the β-hydroxyl group, as in (XII). Inspection of a Stuart model of (IV) shows that hydrogen bonding of this type (XII) is probable on steric grounds and that the three rings (the two five-membered nitrogen-containing rings and the six-membered hydrogen-bonded ring) are approximately equally disposed in space round the common C–C axis. Removal of water involving carbonium-ion formation is presumably assisted by the possibility of resonance of the type $HN\text{–}C^{+}\text{–}NH \longleftrightarrow {}^{+}NH{=}C\text{–}NH$. The zwitterion (XIII) would be expected to lose carbon dioxide readily; the formation of zwitterions as intermediates in the decarboxylation of heterocyclic acids has been postulated on good grounds by Brown and Hammick (*J.*, 1949, 659) and the transitory existence of β-carbonium ions in the decarboxylation of substituted cinnamic acids has been suggested by Johnson and Heinz (*J. Amer. Chem. Soc.*, 1949, **71**, 2913). Decarboxylation produces the zwitterion (XIV) which, it is suggested, is transformed into allantoin by a shift of an electron pair and of a proton from position 5 to position 4.

This last transformation is of course a shift similar in type to that postulated in the Whitmore hypothesis in pinacol, Wagner–Meerwein, and other rearrangements, but it differs from the usual pinacol rearrangement in that it is a hydride ion or an electron pair, and not an alkyl or an aryl group, which migrates. Ingold (" Structure and Mechanism in Organic Chemistry," London, G. Bell & Sons, 1953, p. 474) has already suggested that the frequently observed transformations of αβ-diols to carbonyl compounds without change in the carbon skeleton are essentially pinacol rearrangements. An even closer

analogy to the present case is probably the decarboxylation of an αβ-epoxy-acid to a ketone which is found in the Darzens reaction. This change is best visualized as decarboxylation of a carbonium ion or zwitterion. This proposed mechanism of the transformation of uric acid into allantoin is admittedly speculative, but it explains all the observed facts and the individual steps suggested appear, in the light of other knowledge available, to be reasonable.



Degradation of Uric Acid by Strong Acids.—It was found by Strecker (*Annalen*, 1868, **146**, 1427) that uric acid and concentrated hydrochloric acid at 160—170° yield glycine. Glycine was also obtained under similar conditions from a dimethyluric acid (Mabery and Hill, *Ber.*, 1878, **11**, 1329), later shown to be 3 : 9-dimethyluric acid and also from 9-methyluric acid (Fischer, *Ber.*, 1884, **17**, 1776). The other products obtained from the methyl derivatives were identified as carbon dioxide, ammonia, and methylamine. Fischer (*Ber.*, 1895, **28**, 2480) later obtained sarcosine by hydrolysis of 7-methyluric acid and this clearly showed that the nitrogen atom of the glycine was derived from $N_{(7)}$ of uric acid. Shemin and Rittenberg (*J. Biol. Chem.*, 1947, **167**, 875), in isotope studies on the biogenesis of uric acid in man, used this reaction for the separation of $N_{(7)}$ from the other three nitrogen atoms of uric acid. It is reasonable to assume on the basis of Fischer's observations that the methylene-carbon atom of glycine is derived from $C_{(5)}$, but the carboxyl group could originate from $C_{(4)}$ or $C_{(6)}$ or from both. We have therefore subjected the three types of labelled uric acid to the conditions of hydrolysis first used by Strecker and have determined the radioactivities of the products.

Preliminary experiments with non-labelled uric acid showed that the production of ammonia exceeded the theoretical 3 moles per mole of uric acid. Since glycine was found to be stable under the conditions employed, it follows that the conversion into glycine is accompanied by other, unknown, side reactions. However, no nitrogenous substance other than glycine and ammonia could be detected in the hydrolysates. The calculated yield of glycine, based on liberated ammonia, varied in different experiments between 55% and 75%.

TABLE 3. *Acid hydrolysis of uric acids.**

Starting material and its activity		Activity of $BaCO_3$ from CO_2 released on hydrolysis : obs.	calc.†	Activity of formaldehyde-dimedone derived from glycine CH_2 group : obs.	calc.‡	Activity of $BaCO_3$ derived from glycine-CO_2H group Calc. for origin at : obs.	$C_{(4)}$ only	$C_{(4)}$ and $C_{(6)}$ equally
[4-^{14}C]Uric acid	22,280	16,690	18,550	2800	0	55,000	111,400	55,700
	,,	17,270	,,	2060	,,	56,290	,,	,,
	3800	Not measured		390	0	8700	19,000	9500
[5-^{14}C]Uric acid	8400	690	0	39,330	42,000	1910	0	0
	1400	Not measured		5990	7000	320	0	0
[6-^{14}C]Uric acid	3690	3600	3080	650	0	8870	0	9220
	720	Not measured		70	0	1690	0	1800

* Activities expressed as in Table 1.

† Calc. on the assumption that the glycine-carboxyl is derived from $C_{(4)}$ and $C_{(6)}$ equally (*i.e.*, CO_2 derived from $C_{(2)}$ and $C_{(8)}$ + ½ mole each from $C_{(4)}$ and $C_{(6)}$).

‡ Calc. on the assumption that CH_2O is derived from $C_{(5)}$.

In the isotope experiments the ammonia and carbon dioxide were removed and the glycine without further purification degraded as described above. The radioactivities of the

carbon dioxide formed on hydrolysis, and of the formaldehyde and of the carbon dioxide produced by the degradation of glycine, were measured. The results (Table 3) show that the carbon dioxide samples evolved during the hydrolysis had high activities compared with corresponding uric acid specimens, in the case of both [4-^{14}C]uric acid and [6-^{14}C]uric acid. By comparison with calculated values, the figures suggest that, while $C_{(2)}$ and $C_{(8)}$ give rise to one mol. of carbon dioxide each, $C_{(4)}$ and $C_{(6)}$ produce half a mol. each. The small amount of radioactivity in the carbon dioxide derived from [5-^{14}C]uric acid is almost certainly due to the side-reactions referred to above. The values of the radioactivities of the formaldehyde–dimedone complex and of the barium carbonate derived from the degradation of glycine show clearly that almost all the α-carbon atom of glycine originates from $C_{(5)}$ of uric acid, whilst the carboxyl-carbon atom is derived equally from $C_{(4)}$ and $C_{(6)}$. There is, however, a small amount of radioactivity in the carbonate obtained from [5-^{14}C]-uric acid. This may be due to formation of small amounts (approx. 5%) of glycine by a side reaction. But it is also possible that traces of carbon dioxide and formaldehyde are produced by ninhydrin from an unknown impurity present in the unpurified glycine. However, the main reaction appears to consist of a hydrolysis of uric acid to yield, in the first place, two molecules of carbon dioxide, three of ammonia, and one of aminomalonic acid. The latter is then decarboxylated, to give glycine and a further mole of carbon dioxide which is derived to an approximately equal extent from $C_{(4)}$ and $C_{(6)}$.

Experimental

Counting.—Samples were counted on 1 sq. cm. Polythene discs at "infinite thickness" (Popják, *Biochem. J.*, 1950, **46**, 560), with the exception of some of the formaldehyde–dimedone derivatives, of which the amounts available were insufficient. Appropriate corrections were made to the observed count of these specimens by reference to a standard curve relating weight of sample to activity. The observed counts, corrected where appropriate, were converted into counts per carbon atom at "infinite thickness" on 1 sq. cm. discs by multiplying the sample count by the factor (mol. wt.)/12n, where n = number of carbon atoms in the substance (cf. Cornforth, Hunter, and Popják, *Biochem. J.*, 1953, **54**, 597). To make the results for the formaldehyde–dimedone derivatives comparable with those for barium carbonate n was taken as 1 for these compounds, as only one of the carbon atoms is derived from the labelled substance.

^{14}C-*Labelled Uric Acids.*—These were prepared by the route outlined by Bentley and Neuberger (*loc. cit.*) with certain improvements exemplified in the following preparation of [4-^{14}C]uric acid.

K^{14}CN (20 mg.) was diluted to 6·3 g. with inactive KCN and dissolved in water. The solution was added to a neutralised (Na_2CO_3) solution of bromoacetic acid (13·9 g.) in water, and after 10 min. the mixture was brought to the boil, and boiling continued for 5 min. To the cooled solution was added concentrated hydrochloric acid (10 ml.), and the mixture was taken to dryness at the pump at 60—70°. The residue was extracted with 95% ethanol and the whole was filtered, the residue was re-extracted, and the combined filtrates were evaporated at 40—50° at the pump. To this residue were added 150 ml. of ethanol and 1 ml. of concentrated sulphuric acid, and the whole was boiled under reflux for 3 hr., cooled, filtered, and concentrated. The residue was neutralised with aqueous sodium carbonate and twice extracted with benzene. The combined extracts after drying (Na_2SO_4) were fractionally distilled in a vacuum, to give 7·9 g. (70%) of $^{14}CN{\cdot}CH_2{\cdot}CO_2Et$ (cf. Inglis, *Org. Synth.*, Coll. Vol. I, 2nd edn., p. 254).

The labelled cyanoacetic ester was diluted with inactive ester to 11·3 g. and converted by Bogert and Davidson's procedure (*J. Amer. Chem. Soc.*, 1933, **55**, 1667) into diaminouracil sulphate (11·8 g., 57%). The following procedure for the conversion of diaminouracil sulphate into uric acid (without the necessity for isolating free diaminouracil) had considerable advantages over the procedure of Johnson and Johns (*J. Amer. Chem. Soc.*, 1914, **36**, 545): Diaminouracil sulphate (4·8 g.) and urea (14 g.) were powdered together and then heated in a sealed tube for 1 hr. at 180°. The tube contents were extracted with water. The extract was discarded, and the residue was taken up in hot aqueous sodium hydroxide, filtered, and acidified with hydrochloric acid, to precipitate uric acid (4·15 g., 98% based on diaminouracil sulphate). The product was considerably cleaner than when the Johnson–Johns procedure was used, but was recrystallised from a large volume of boiling water (charcoal) to give almost colourless crystals (85% recovery), the purity of which was checked spectroscopically (cf. Bentley and Neuberger,

loc. cit.). The [4-^{14}C]uric acid so obtained had an activity of 7952 counts per min. per 1 sq. cm. disc.

By similar methods, using bromoacetic acid labelled in the methylene or carboxyl groups (obtained from the Radiochemical Centre, Amersham) there were obtained [5-^{14}C]uric acid and [6-^{14}C]uric acid with activities of 2998 and 1318 counts per min. per 1 sq. cm. disc, respectively. Uric acids labelled with ^{14}C predominantly, but not exclusively, in the 4, 5, or 6 position have previously been prepared biosynthetically by injecting suitably labelled precursors into pigeons (Karlsson and Barker, *J. Biol. Chem.*, 1949, **177**, 597). More recently Brandenberger (*Helv. Chim. Acta*, 1954, **37**, 641) has prepared [6-^{14}C]uric acid by a similar method and [4-^{14}C]uric acid from the corresponding labelled hypoxanthine.

Acid Hydrolysis of Uric Acid.—Unlabelled uric acid (0·25 g.), concentrated hydrochloric acid (6 ml.), and water (3 ml.) were heated for 20 hr. at approx. 185—200°. The tube contents (CO_2 evolution) were taken to dryness in a vacuum on the water-bath, water was added, the whole again evaporated to dryness, and the residue made up to 50 ml. with water. The immediate formation of a clear solution in water showed the complete destruction of uric acid. The amount of ammonia in the hydrolysate was estimated in triplicate on 2-ml. aliquot portions by the micro-Kjeldahl technique of Markham (*Biochem. J.*, 1942, **36**, 790). The number of N atoms liberated as ammonia from each molecule of uric acid was found in four experiments to be 3·24, 3·39, 3·42, 3·44. In control experiments glycine (100 mg.) was treated in the same way and no ammonia was found after "hydrolysis." Ammonia in excess of 3 atoms per molecule is not therefore due to breakdown of preformed glycine. Paper chromatography of the uric acid hydrolysate showed the presence of glycine, but of no other substance reacting with ninhydrin. Neither was there any indication of material absorbing ultra-violet light. A sample of the ammonia formed on hydrolysis was kindly examined by Dr. A. T. James by the gas-partition chromatographic procedure of James and Martin (*Biochem. J.*, 1952, **51**, 323). Only ammonia, and in particular no methylamine, was found to be present.

Hydrolysis was then carried out in the same way on samples of [4-^{14}C]-, [5-^{14}C]-, and [6-^{14}C]-uric acid. When cool the tubes were frozen in liquid air, opened, and quickly transferred to an apparatus swept with CO_2-free nitrogen. The tubes were allowed to warm slowly, the evolved gases passing through saturated silver sulphate solution to remove any hydrogen chloride and then through saturated barium hydroxide solution. The barium carbonate was collected in the usual way and counted. After liberation of carbon dioxide the residual aqueous solution was taken to dryness, redissolved, again taken to dryness, and then taken up in phosphate buffer, pH 5·5 (K_3PO_4 3·5 g. and KH_2PO_4 20 g./100 ml.; cf. Arnstein, *Biochem. J.*, 1951, **49**, 439). The glycine in the hydrolysate was degraded with ninhydrin as described by Arnstein (*loc. cit.*), the methylene group of glycine being counted as formaldehyde–dimedone complex and the carboxyl group as barium carbonate. The formaldehyde–dimedone complex specimens were recrystallised from aqueous ethanol.

Stepwise Degradation of Uric Acid via *Allantoin.*—Labelled uric acid (*ca.* 0·2 g.; weighed accurately) was diluted with unlabelled uric acid (*ca.* 1·8 g.; weighed accurately) and converted into allantoin (1·5 g. after recrystallisation from water) by the method of Hartmann, Moffett, and Dickey (*Org. Synth.*, Coll. Vol. II, p. 21). Activities of the products are summarised in Table 2. The complete absence of activity in the allantoin from [6-^{14}C]uric acid shows that no appreciable amount of uroxanic acid or other undecarboxylated product can be present in material prepared by this method.

Allantoin (2 g. of labelled, or 1 g. of labelled diluted with 1 g. of unlabelled) was converted into hydantoin by reductive hydrolysis with phosphonium iodide (Gillespie and Snyder, *Org. Synth.*, Coll. Vol. II, p. 489), giving 0·5 g. of recrystallised hydantoin, decomp. 220—222°. The absence of glycine and allantoin was confirmed by paper chromatography. Activities of the products are summarised in Table 2.

The hydantoin was refluxed with 50 ml. of *ca.* N-sodium hydroxide (a considerable excess) for 40 hr. The solution was cooled, filtered, shaken with benzoyl chloride (x ml., where $x = 1{\cdot}25$ times the weight of initial hydantoin in g.), acidified with concentrated hydrochloric acid, and set aside at 0°. The hippuric acid was separated from the benzoic acid by a procedure similar to that described by Arnstein (*loc. cit.*). The precipitated material, after drying, was twice extracted with light petroleum (b. p. 60—80°), and the mother-liquors were twice extracted with toluene. The mother-liquors were then extracted three times with ethyl acetate, the combined ethyl acetate extracts were dried (Na_2SO_4), and the solvent was evaporated. The residue was combined with the solid residue from the light petroleum extraction of the original precipitate, and the combined solids were recrystallised from ethanol. The purity of the

resultant hippuric acid was confirmed by m. p., and in two cases (experiments 3 and 4) by counting. In these cases the observed counts were 134 and 263, and the calculated counts were 137 and 268 counts per min. per 1 sq. cm. disc respectively.

The hippuric acid (approx. 300 mg.) was hydrolysed by refluxing with 1 : 1 concentrated hydrochloric acid for 20 hr. The cooled hydrolysate was diluted and extracted once with ethyl acetate and twice with ether. The aqueous fraction was taken down to dryness at the pump on the water-bath, and the resultant glycine degraded with ninhydrin as previously described. These results are summarised in Table 3.

National Institute for Medical Research, Mill Hill, London, N.W.7.
Postgraduate Medical School, Ducane Road, London, W.12. [*Received, 7th May*, 1954.]

The Oxidation of Monoethenoid Fatty Acids and Esters. Catalytic Oxidation of n-*Propyl Oleate. The Oxidation Products.*

By A. J. Feuell and J. H. Skellon.

[Reprint Order No. 5374.]

The products of catalytic oxidation at 55°, 85°, and 120° of *n*-propyl oleate by gaseous oxygen have been resolved. The main products resulting from transformation or decomposition of the initially formed hydroperoxides are 9 : 10-epoxy- and 9 : 10-dihydroxy-stearic acids, unsaturated keto-esters, and the scission fragments nonanoic, decanoic, suberic, and azelaic acid. With increasing temperature and duration of oxidation, the unsaturated keto-esters tend to dimerise and form oils and resins that still retain their ketonic character.

The observed rapid loss of unsaturation at the higher temperatures, and the formation of appreciable quantities of epoxy- and dihydroxy-stearic acid derivatives, are compatible with a mechanism involving direct attack on ethenoid linkages by free hydroxyl radicals generated by thermal homolytic fission of the initially formed hydroperoxides.

Feuell and Skellon (*J.*, 1952, 59) found that, on the catalytic oxidation of *n*-propyl oleate by gaseous oxygen, maximum peroxidation with rapid loss of unsaturation occurred at 85—120°. Detailed investigation of the numerous products of similar oxidations is now described.

Purified *n*-propyl oleate (Feuell and Skellon, *loc. cit.*) was catalytically oxidised, with high oxygen dispersion and uranium oleate as catalyst (Skellon and Spence, *J. Soc. Chem. Ind.*, 1948, **67**, 365; Skellon and Thruston, *J.*, 1953, 138) to achieve rapid peroxidation. The conditions were generally similar to those previously employed (Feuell and Skellon, *loc. cit.*), but the oxidations extended over longer periods to secure reasonable yields of the end-products resulting from hydroperoxide decomposition. The oxidation products were separated by solvent fractionation, crystallisation, and distillation, methods previously described being suitably modified (Skellon, *J. Chem. Soc. Ind.*, 1931, **50**, 382T; *J.*, 1948, 343; Ellis, *Biochem. J.*, 1936, **30**, 753; 1950, **46**, 129).

Carbon dioxide was evolved during the oxidations, but even under the most stringent conditions the amount of chain degradation ($CH_2 \longrightarrow CO_2 + H_2O$) was small, corresponding to less than 0·5 atom of carbon per molecule of ester. The quantities of water were in all cases considerably in excess of those equivalent to the amount of carbon dioxide required by the above reaction, and apparently resulted from hydroperoxide decomposition to αβ-unsaturated ketones or to epoxide formation from dihydroxystearic acid derivatives.

The principal substances obtained were 9 : 10-epoxy- and 9 : 10-dihydroxy-stearic acids, oily and resinous ketonic products, and the scission fragments nonanoic, decanoic, suberic, and azelaic acids. The dihydroxy-stearic acid was isolated principally as the *threo*-isomer (m. p. 95°), but after prolonged oxidation (18 hr.) at 120°, much of this compound was obtained initially in the form of a complex of high molecular and equivalent weight that was converted into the *erythro*-isomer (m. p. 132°) by strong alkaline hydrolysis.

There was evidence for the presence of polymerised semi-aldehydes of suberic and azelaic acid. Small amounts of volatile lower fatty acids were detected. Prolonged oxidation at 120° resulted in the formation of a little hydroxyoxostearic acid (mixture of 9 : 10- and 10 : 9-isomers). Mild alkaline hydrolysis of the oxidised esters gave small yields of a mixture of nonanal and nonan-2-one, affording evidence for the presence of unsaturated

(I) $CH_3{\cdot}[CH_2]_6{\cdot}CO{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2Pr$ $CH_3{\cdot}[CH_2]_7{\cdot}CH{:}CH{\cdot}CO{\cdot}[CH_2]_6{\cdot}CO_2Pr$ (II)

keto-esters (I and II), as suggested by Ellis (*loc. cit.*). Hydrolysis of (I) yields azelaic ester semialdehyde and nonan-2-one, while (II) gives nonanal and 8-oxononanoic ester. The yields of the principal end-products resolved are given in the Table.

Products of catalytic oxidation of n-*propyl oleate* (g. per 100 g. of oxidised ester).

Temperature	55°	85°	120°	120°
Time of oxidation (hr.)	50	45	8	18
Products :				
9 : 10-Dihydroxystearic acid	3·1	9·6	7·4	17·1
9 : 10-Epoxystearic acid	8·3	4·1	2·2	9·5
9 : 10- and 10 : 9-Hydroxyoxostearic acid	—	—	—	2·1
Nonanoic acid	0·8	3·7	1·4	3·1
Decanoic acid	—	1·3	3·1	3·1
Suberic acid	—	1·4	0·7	1·8
Azelaic acid	0·3	2·4	1·0	2·2
$\alpha\beta$-Unsaturated keto-esters	0·4	1·6	1·8	1·5
Ketonic oils (sol. in light petroleum)	6·3	14·8	12·3	3·4
Ketonic resins (insol. in light petroleum)	1·4	16·9	22·7	28·8

The results are compatible with Waters's suggestion (*Ann. Reports*, **1945**, 134) that during oxidations, particularly at the higher temperatures, some of the hydroperoxide formed initially by the α-methylenic chain-reaction sequence (Farmer, *Trans. Faraday Soc.*, 1946, **42**, 233; Bawn, *J. Oil Col. Chem. Assoc.*, 1953, **36**, 443) undergoes homolytic fission :

$$-\underset{\underset{O{\cdot}OH}{|}}{CH}-CH{=}CH-CH_2- \longrightarrow -\underset{\underset{O{\cdot}}{|}}{CH}-CH{=}CH-CH_2- + {\cdot}OH$$

The observed rapid loss of unsaturation at high temperatures, and the formation of appreciable quantities of 9 : 10-epoxy- and 9 : 10-dihydroxy-stearic acid, are explained by the attack on ethenoid linkages by the free hydroxyl radicals so formed :

$$-CH{=}CH- + {\cdot}OH \longrightarrow -\underset{\underset{OH}{|}}{CH}-\underset{\underset{\cdot}{|}}{CH}- + {\cdot}OH \longrightarrow -\underset{\underset{OH}{|}}{CH}-\underset{\underset{OH}{|}}{CH}- \text{ or } -\underset{\diagdown\,O\,\diagup}{CH}-CH- + H_2O$$

The process of thermal catalytic oxidation appears to involve : (1) Decomposition of the hydroperoxides in the presence of the metallic catalyst (uranium), yielding αβ-unsaturated ketonic esters (cf. Cook, *J.*, 1938, 1774; Paquot, *Bull. Soc. chim.*, 1945, **12**, 120) :

$$-\underset{\underset{O{\cdot}OH}{|}}{CH}-CH{=}CH-CH_2- \longrightarrow -CO-CH{=}CH-CH_2- + H_2O$$

(2) Fission of the isomeric hydroperoxides to mono- and di-basic acids and the semi-aldehydes of the latter (Gibson, *J.*, 1948, 2275). The αβ-unsaturated ketonic esters may subsequently dimerise or polymerise to form the oily resins that are always obtained in appreciable quantities from such oxidations.

Experimental

Preparation of n-*Propyl Oleate.*—Purified oleic acid was prepared from olive oil (Skellon, *J. Soc. Chem. Ind.*, 1931, **50**, 131T) and converted into the *n*-propyl ester (Feuell and Skellon, *loc. cit.*) (Found : sap. val., 175·0; I val., 75·7. Calc. for $C_{21}H_{40}O_2$: sap. val., 172·9; I val., 78·2).

Catalytic Oxidations.—General. Oxygen at 18 mm. pressure was passed into the ester (45 g.) contained in a small bulb fitted with a stopper through which passed a No. 4 sintered-glass

bubbler (for oxygen), a thermometer, a stoppered tube (for a sampling pipette), and an exit tube. The apparatus was placed in a thermostatically controlled oven, and the exit gases were passed through a weighed U-tube cooled in ice and through concentrated sodium hydroxide solution. All oxidations were carried out in the presence of 0·05% of uranium (as uranyl oleate dissolved in the ester).

Oxidation at 55°. The ester was oxidised for 50 hr. Water (0·093 g.) and a trace of sharp-smelling oil were collected in the U-tube. Carbon dioxide (0·122 g.) was evolved steadily throughout. Changes in peroxide content were :

Time (hr.)	4	8	22	32	46	50
Active O (%) *	0·098	0·137	0·273	0·314	0·423	0·465

* Method of Skellon and Wills (*Analyst*, 1948, **73**, 78).

The oxidised product had the following characteristics : sap. val., 183·1; acid val., 9·1; I val., 65·6; *M* (Rast), 330; CO (Method of Skellon and Feuell, *Analyst*, 1953, **78**, 135), 1·62%.

Oxidation at 85°. The ester was oxidised for 45 hr. Water (0·87 g.) and a trace of aldehyde (Schiff's test) were collected. Carbon dioxide (1·56 g.) was evolved throughout, the evolution being greater during the later stages. Changes in peroxide content were :

Time (hr.)	4	12	20	24	37	45
Active O (%)	0·397	0·964	1·230	1·218	0·775	0·621

The oxidised product had the following characteristics : sap. val., 261·5; acid val., 70·5; I val., 16·3; CO, 2·76%; *M* (Rast), 374.

Oxidation at 120°. The ester was oxidised for 8 and 18 hr. In the first run, 1·30 g. of water were collected, and in the second 3·43 g. Carbon dioxide (0·94 and 2·84 g. respectively) was evolved, the evolution being greatest after 8—12 hours' oxidation. Changes in peroxide content were :

Time (hr.)	1	2	3	4	6	8	12	18
Active O (%) (8 hr.)	0·471	0·621	0·604	0·585	0·435	0·318	—	—
„ (18 hr.)	—	0·618	—	0·640	0·562	—	0·440	0·258

The oxidised products from the 8 and the 18 hr. runs had the following characteristics, respectively : sap. val., 250·0, 311·2; acid val., 58·1, 58·0; I val., 26·0, 8·7; CO, 1·70, 1·42%; *M* (Rast), 368, 405.

Detailed Analysis of the Oxidised Esters.—(a) *Resolution into acidic and neutral fractions.* The products (*ca.* 40 g.) from the four oxidations [denoted below as : 55°, A; 85°, B; 120° (8 hr.) C; 120° (18 hr.) D] in ether (100 ml.) were extracted thrice with 20% sodium carbonate solution. After being washed with ether, the alkaline extracts were refluxed with excess of alcoholic N-potassium hydroxide, then acidified with hydrochloric acid, and the mixed liberated acids extracted with ether. Material A yielded 1·3 g., B 7·25 g., C 7·9 g., and D 7·6 g., of brown acids (Found, respectively : equiv., 235·1, 138·6, 263·5, 149·3; I val., 63·0, 11·8, 18·3, 9·5). The aqueous layer after extraction of these acids was neutralised, re-acidified with sulphuric acid, and distilled in steam; the distillates from B, C, and D were sharp-smelling and required for neutralisation, respectively, 4·2, 6·3, 7·1 ml. of 0·05N-alkali. On recovery of the neutral oxidation products, A afforded 33·7 g., B 28·6 g., C 27·0 g., and D 31·6 g. of yellow oils (Found, respectively : sap. val., 175·2, 204·0, 190·5, 241·4; I val., 65·7, 17·4, 30·8, 7·7). During extraction, ether-insoluble *n*-propyl dihydroxystearate separated : B gave 0·61 g. and C 0·7 g. of the *threo*-isomer, m. p. (recrystallised) and mixed m. p. 58—59° (lit., 59°) (Found, respectively : sap. val., 156·5, 159·9. Calc. for $C_{21}H_{42}O_4$: sap. val., 156·5); hydrolysis gave *threo*-9 : 10-dihydroxystearic acid, m. p. and mixed m. p. 94—95° (lit., 95°) (Found : equiv., 315·5. Calc. for $C_{18}H_{36}O_4$: equiv., 316·5). Material D gave 2·0 g. of impure *erythro*-isomer, m. p. (recrystallised) and mixed m. p. 92—93° (lit., 94°) (Found : sap. val., 158·6); hydrolysis gave *erythro*-9 : 10-dihydroxystearic acid, m. p. and mixed m. p. 132° (lit., 132°) : impure *threo*-isomer (0·2 g.), m. p. 65—68°, was obtained from the mother-liquor after recrystallisation.

(b) *Separation of the acidic products.* The acids were refluxed four times with light petroleum (b. p. 40—60°), and the combined concentrated extracts cooled at 0° : the precipitates of impure dibasic acids (A 0·07 g., B 1·1 g., C 0·4 g., D 1·2 g.) were removed by filtration. Extraction of the light-petroleum-insoluble residues with hot 25% ethanol gave further small yields of impure dibasic acids that were combined with the main precipitates and purified with ethanol and chloroform, affording suberic and azelaic acids : B gave 0·7 g. of suberic acid, C 0·2 g., D 0·5 g., having, respectively, m. p. (recrystallised) and mixed m. p., 139°, 140°, 139—140°

(lit., 140°) (Found, respectively: equiv., 88·5, 88·0, 87·8. Calc. for $C_8H_{14}O_4$: equiv., 87·1); A gave 0·07 g. of azelaic acid, B 1·2 g., C 0·3 g., D 0·8 g., having, respectively, m. p. (recrystallised) and mixed m. p. 104—105°, 106°, 105—106°, 105—106° (lit., 106°) (Found, respectively: equiv., 94·1, 94·9, 93·9, 94·0. Calc. for $C_9H_{16}O_4$: equiv., 94·1).

The light petroleum liquors gave, on evaporation, sharp-smelling yellow oils, which were steam-distilled. The oily distillates, extracted with ether, afforded an acid: from A 0·2 g., B 1·1 g., C 0·2 g., D 0·7 g. (Found, respectively: equiv., 160·0, 155·7, 160·0, 156·2. Calc. for $C_9H_{18}O_2$: equiv., 158·2), presumed to consist mainly of nonanoic acid. The oily residues not volatile in steam, by treatment with 40% ethanol, yielded decanoic acid and some unchanged oleic acid: B gave 1·1 g. of impure decanoic acid, C 1·1 g., D 0·77 g., having, respectively, f. p. (purified) 29—30°, 30—32°, 30—31° (lit., 31·5°) (Found, respectively: equiv., 174·0, 170·5, 173·0. Calc. for $C_{10}H_{20}O_2$: equiv., 172·2); A gave 0·5 g. of oleic acid, B 0·8 g., C 2·7 g. (Found, respectively: equiv., 283·8, 278·5, 280·5; I val., 89·9, 85·7, 87·8. Calc. for $C_{18}H_{34}O_2$: equiv., 282·5; I val., 89·9).

The acids insoluble in hot light petroleum, after extraction with 25% ethanol, formed brown resins (thought to be polymers of azelaic semialdehyde): from B 1·98 g., C 2·3 g., D 2·5 g. [Found, respectively: equiv., 156·6, 164·7, 190·4; *M* (Rast), 612, 807, 461; OH, 4·7, 4·7, 4·2; CO, 3·7, 3·3, 2·9; C, 66·8, 63·1, 62·3; H, 10·3, 8·8, 9·1%. Calc. for $(C_9H_{16}O_3)_n$: equiv., 172·2; *M* ($n = 4$), 688·8; OH, 7·41; CO, 4·1; C, 62·8; H, 9·3%].

(c) *Resolution of the neutral substances.* The neutral oils (*ca.* 30 g.) were refluxed with 0·05N-sodium hydroxide (750 ml.) for 2 hr. (Ellis, *Biochem. J.*, 1950, **46**, 129), and the small yields of volatile products were collected [see (d) below]. The esters recovered from this mild hydrolysis were completely saponified with N-potassium hydroxide in 50% alcohol, and after acidification and ether-extraction yielded mixed free acids: from A 28 g., B 27 g., C 22 g., D 13 g. (Found, respectively: equiv., 282·1, 274·4, 271·2, 287·4; I val., 80·7, 28·3, 30·6, 10·1). Material D also gave 2 g. of an ether-insoluble white solid, m. p. 175—180° (Found: equiv., 664), which after hydrolysis with alcoholic 3N-potassium hydroxide for 3 hr. afforded *erythro*-9: 10-dihydroxystearic acid, m. p. and mixed m. p. 131—132° (lit., 132°) (Found: equiv., 315·7. Calc. for $C_{18}H_{36}O_4$: equiv., 316·5).

The mixed free acids were dissolved in 3—4 times their bulk of 96% methanol and cooled at 0°. The precipitates were fractionated with *n*-hexane into insoluble and soluble fractions, consisting of 9: 10-epoxystearic and unchanged oleic acid respectively. Material A gave 2·9 g. of epoxide, B 1·4 g., C 1·7 g., D 2·2 g., m. p.s 53—54° (lit., 55°) (Found, respectively: equiv., 298·5, 297·8, 297·2, 298·0. Calc. for $C_{18}H_{34}O_3$: equiv., 298·5) [partly hydrolysed by 40% potassium hydroxide to *erythro*-9: 10-dihydroxystearic acid, m. p. 131° (lit., 132°)]. The yields of oleic acid were: from A 2·0 g., B 1·5 g., C 0·9 g., D 0·2 g. (Found, respectively: equiv., 283·1, 281·1, 283·3, —; I val., 87·2, 88·4, 88·4, 86·9. Calc. for $C_{18}H_{34}O_2$: equiv., 282·5; I val., 89·9).

The methanolic filtrates remaining after removal of the impure epoxide precipitates were carefully diluted with warm water, and the separated oils washed with dilute methanol and hot water, all washings being bulked. At this stage, 0·8 g. of *threo*-9: 10-dihydroxystearic acid was deposited from D; it had m. p. (recrystallised) and mixed m. p. 94° (lit., 95°) (Found: equiv., 314·8. Calc. for $C_{18}H_{36}O_4$: equiv., 316·5). The combined dilute methanolic liquors were made just alkaline, concentrated, acidified with sulphuric acid, and steam-distilled; the oily distillates, extracted with ether, yielded nonanoic acid: from A 0·08 g., B 0·2 g., C 0·3 g., D 0·06 g. (Found, respectively: equiv., 163·7, 160·5, 159·7, 163·9. Calc. for $C_9H_{18}O_2$: equiv., 158·2). The solid residues not volatile in steam were extracted with hot benzene and gave small yields of impure dibasic acids (suberic and azelaic acids): from B 0·3 g., C 0·5 g., D 0·3 g. (Found, respectively: equiv., 92·7, 91·8, 98·1. Calc. for $C_8H_{14}O_4$: equiv., 87·1. Calc. for $C_9H_{16}O_4$: equiv., 94·1). The separated and washed oils after drying (from A 20·5 g., B 18·2 g., C 18·0 g., D 9·9 g.) were refluxed four times with light petroleum (b. p. 40—60°), and the combined concentrated extracts cooled at 0°; the precipitates of impure *threo*-9: 10-dihydroxystearic acid were removed by filtration: A gave 1·1 g., B 1·9 g., C 1·6 g., D 1·5 g., m. p. (recrystallised) and mixed m. p. 93—95° (lit., 95°) (Found, respectively: equiv., 315·1, 316·9, 315·7, 317·1. Calc. for $C_{18}H_{36}O_4$: equiv., 316·5). The precipitate from material D only, on treatment with light petroleum and chloroform (King, *J.*, 1936, 1788) gave 0·5 g. of hydroxyoxostearic acid, m. p. 62—63°, mixed m. p. 63—64° (lit., 64—65°) (mixture of 9: 10- and 10: 9-isomers) (Found: equiv., 313·1. Calc. for $C_{18}H_{34}O_4$: equiv., 314·5); it gave mixed semicarbazones of m. p. 135—138° (lit., 130—140°).

The light petroleum mother-liquors afforded, on evaporation, pale yellow oils: from A

19·0 g., B 8·9 g., C 6·2 g., D 0·8 g. These oils, by repeated treatment with acetone at −20°, were separated into unchanged oleic acid and ketonic oils of dimeric nature. Material A yielded 15·0 g. of oleic acid, B 3·1 g., C 1·3 g. (Found, respectively: equiv., 283·3, 284·0, 280·3; I val., 87·1, 87·4, 87·9. Calc. for $C_{18}H_{34}O_2$: equiv., 282·5; I val., 89·9). The yields of ketonic oils were: from A 2·2 g., B 5·1 g., C 4·4 g., D 0·8 g. These oils were subjected to steam-distillation and extraction with 30% ethanol to remove monomeric products before analysis [Found, respectively: equiv., 323·4, 337·0, 289·5, 288·5; I val., 48·7, 42·3, 39·3, 18·7; OH, 0·71, 0·90, 0·87, 1·41%; CO, 2·03, 1·48, 2·27, 2·47%; *M* (Rast), 402, 443, 458, 471].

The residues insoluble in hot light petroleum after extraction with 30% alcohol formed brown resins: from A 0·5 g., B 5·8 g., C 8·1 g., D 6·7 g. [Found, respectively: equiv., 323·1, 293·6, 268·5, 324·0; I val., 42·0, 33·3, 28·8, 15·3; OH, —, —, 5·23, 5·96; CO, 1·93, 1·79, 1·93, 1·34%; *M* (Rast), 474, 504, 423, 519].

(d) *Examination of volatile products of mild hydrolytic distillation.* The volatile products from the initial mild hydrolysis of the neutral substances were sharp-smelling oils: from A 0·04 g., B 0·18 g., C 0·21 g., D 0·15 g.; they gave positive Schiff's tests and formed 2 : 4-dinitrophenylhydrazones of m. p., respectively, 57—59°, 70—73°, 67—70°, 72—75°. A similar oily distillate (2·5 g.) from the hydrolysis of 100 g. of *n*-propyl oleate oxidised at 85° for 28 hr. contained 8·3% of free acid calculated as nonanoic acid; it yielded a 2 : 4-dinitrophenylhydrazone of m. p. 72—75°. This oil was treated with excess of moist silver oxide, made alkaline, and extracted with ether; on evaporation 0·9 g. of nonan-2-one was obtained; the m. p. and mixed m. p. of the derived semicarbazone was 119° (lit., 119°), and of the 2 : 4-dinitrophenylhydrazone 37—39° (authentic specimen, 39°). The alkaline liquors after ether-extraction were acidified and steam-distilled; the volatile product (1·2 g.) consisted of nonanoic acid (Found: equiv., 157·9. Calc. for $C_9H_{18}O_2$: equiv., 158·2); it formed a zinc salt having m. p. and mixed m. p. 131—132° (lit., 130—132°).

CHEMISTRY DEPARTMENT, ACTON TECHNICAL COLLEGE,
HIGH STREET, ACTON, LONDON, W.3.

[*Received, May 7th*, 1954.]

Steroids and Walden Inversion. Part XV. The Mechanism and Stereochemical Course of Some Grignard Carboxylations and Oxygenations.*

By G. ROBERTS and C. W. SHOPPEE.

[Reprint Order No. 5380.]

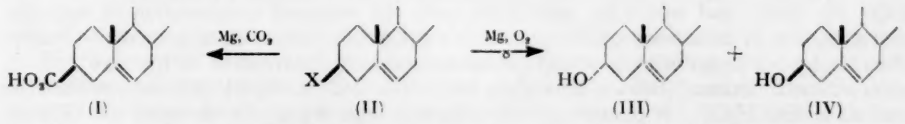
Grignard carboxylation of cholesteryl chloride or bromide has been shown to give only cholest-5-ene-3β-carboxylic acid, but, as we have confirmed, Grignard oxygenation affords approximately equimolecular quantities of *epi*-cholesterol and cholesterol. Similarly, whereas Grignard carboxylation of *epi*cholestanyl bromide or cholestanyl bromide has been shown to give uniquely cholestane-3β-carboxylic acid, Grignard oxygenation of either bromide furnishes the same approximately equimolecular mixture of *epi*-cholestanol and cholestanol.

The mechanisms of the formation of Grignard compounds and of their reactions with carbon dioxide and oxygen are discussed.

CHOLESTERYL CHLORIDE or bromide (II; X = Cl or Br) by treatment with magnesium and carbon dioxide gives a single acid, which we have shown to be cholest-5-ene-3β-carboxylic acid (I) (Roberts, Shoppee, and Stephenson, *J.*, 1954, 2705). Cholesteryl chloride (II; X = Cl), however, by treatment with magnesium and oxygen, gives an approximately equimolecular mixture of *epi*cholesterol (III) and cholesterol (IV) (Marker *et al.*, *J. Amer. Chem. Soc.*, 1936, **58**, 481, 1948), as we have confirmed. *epi*Cholesterol cannot arise from cholesterol in the proportion found because the latter is unaffected under the conditions of Grignard oxygenation, and the equilibrium mixture consists of ~10% of *epi*cholesterol and ~90% of cholesterol (Barnett, Heilbron, Jones, and Verrill, *J.*, 1940, 1390). Cholest-5-ene-3β-carboxylic acid could arise from the 3α-carboxylic acid since the

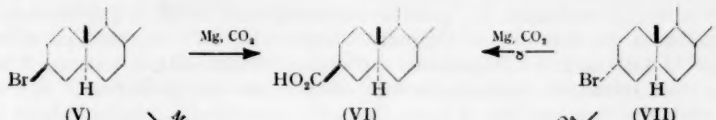
* Part XIV, *J.*, 1954, 3178.

equilibrium mixture consists of ~5% of 3α-carboxylic acid and ~95% of 3β-carboxylic acid, but we have found that cholest-5-ene-3α-carboxylic acid is not epimerised under the conditions of Grignard carboxylation. One reaction thus proceeds with retention of configuration at $C_{(3)}$ and the other with racemisation at $C_{(3)}$.



(I) (II) (III) (IV)

Cholestanyl bromide (V) and *epi*cholestanyl bromide (VII) furnish uniquely the same cholestane-3β-carboxylic acid (VI) by Grignard carboxylation (Roberts, Shoppee, and Stephenson, *loc. cit.*); we now find that both these bromides by Grignard oxygenation afford an approximately equimolecular mixture of *epi*cholestanol (VIII) and cholestanol (IX). Cholestane-3β-carboxylic acid (VI) could arise from cholestane-3α-carboxylic acid; but the equilibrium mixture contains 25—30% of the latter acid (Roberts, Shoppee, and Stephenson, *loc. cit.*), yet none could be isolated. Moreover, cholestane-3α-carboxylic acid is not epimerised under the conditions of Grignard carboxylation. *epi*Cholestanol (VIII) cannot be derived from cholestanol (IX) in the proportion found since the equilibrium



(V) (VI) (VII)

(VIII) (IX)

From V : 51%
From VII : 47%

From V : 49%
From VII : 53%

mixture consists of ~10% of (VIII) and ~90% of (IX) (Windaus and Uibrig, *Ber.*, 1914, **47**, 2384). One Grignard carboxylation (V ⟶ VI) thus proceeds with retention, and the other (VII ⟶ VI) with inversion at $C_{(3)}$, whilst both Grignard oxygenations occur with racemisation at $C_{(3)}$.

It seems of interest briefly to examine the mechanism and stereochemistry of the above Grignard carboxylations :

$$R{\cdot}X \xrightarrow{(a)} R{\cdot}MgX \xrightarrow{(b)} R{\cdot}CO_2{\cdot}MgX$$

Reaction (*a*) occurs at the magnesium surface and could, in principle, give the carbonium ion R^+, the radicle R·, or the carbanion R^-; reaction (*b*) occurs in the absence of a metallic surface, and is generally held to involve the carbanion R^- (cf. Ingold, "Structure and Mechanism in Organic Chemistry, Bell, London, 1953, 787), either free or as an ion pair, $R^-\}MgX^+$, in a non-polar solvent.

The formation of R·MgX appears to involve complete fission of the carbon–halogen bond, because (+)- and (−)-methyl-*n*-hexyl bromide both yield completely racemised methyl-*n*-hexylmagnesium bromide (Porter, *J. Amer. Chem. Soc.*, 1935, **57**, 1436). Production of a planar carbonium ion (sp^2-hybridisation with a vacant *p*-orbital) would be consistent with the formation of completely racemised Grignard derivatives from optically active halides; it apears to be excluded * by the reaction of *neo*pentyl bromide and magnesium, because treatment with carbon dioxide or phenyl *iso*cyanate yields ββ-di-

* Failure of cholesteryl bromide to give **3** : 5-*cyclo*cholestane-6β-carboxylic acid by Grignard carboxylation also tends to exclude production of the cholest-5-en-3β-yl cation.

methylbutyric acid or its anilide (Whitmore and Fleming, *ibid.*, 1933, **55**, 4161), whereas rearrangement to the *tert.*-amyl structure always occurs in reactions involving the *neo*-pentyl cation (Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173). Production of a radical is known to take place in the exceptional and specially favourable case of the formation of triphenylmethylmagnesium bromide (Gomberg and Bachmann, *J. Amer. Chem. Soc.*, 1930, **52**, 2435), and would be compatible with the observed racemisation of optically active halides by treatment with magnesium because the conversion of primary (+)-amyl chloride by both photochemical and peroxide-catalysed chlorination to inactive 1 : 2-dichloro-2-methylbutane (Brown, Kharasch, and Chao, *ibid.*, 1940, **62**, 3435) shows that the radical $MeEt(CH_2Cl)C\cdot$ is planar (sp^2-hybridisation with a single *p*-electron) (cf. Gilman, " Organic Chemistry, 2nd edn., Vol. I, p. 383 *et seq.*, John Wiley and Sons Inc., New York, 1943). It would also be consistent with the production from *neo*pentyl iodide in the Wurtz reaction with sodium of the unrearranged products *neo*pentane and 1 : 1-dimethyl-*cyclo*propane unaccompanied by the expected rearranged products *iso*pentane and trimethylethylene (Whitmore, Popkin, and Pfister, *ibid.*, 1939, **61**, 1616), but neither in their formation nor in their reactions do Grignard reagents generally exhibit the characteristic behaviour of radicals.* Thus, dimerisation normally leads only to unimportant by-products, but in the presence of appropriate catalysts, *e.g.*, cobaltous chloride, reactions characteristic of radicals such as dimerisation, dismutation, and abstraction of hydrogen from the medium become very prominent.

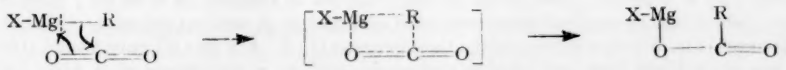
We believe that a carbanion R^-, possibly as an ion pair $R^-\}MgX^+$, is involved in both the formation and the reactions of Grignard compounds. We suggest that a carbanion has a preferred tetrahedral configuration (sp^3-hybridisation with a lone pair) separated from the inverse tetrahedral arrangement by only a low energy barrier; this would be consistent with the racemisation of optically active saturated aliphatic halides by treatment with magnesium (cf. Gilman, *op. cit.*). Sidgwick (" The Chemical Elements and their Compounds," Vol. I, xix *et seq.*, Oxford Univ. Press, 1950), and Lennard-Jones *et al.* (*Proc. Roy. Soc.*, 1949, *A*, **198**, 1, 14; 1950, *A*, **202**, 155, 166, 323, 336) have stressed the importance of lone pairs and the Cambridge authors have concluded that " lone pairs may be important factors in determining equilibrium configurations of molecules; " presumably this conclusion must extend to carbanions, in which the unshared electron pair may be expected to occupy an orbital of at least the same size as, and of possibly larger size than, a C–H bond.† It has been observed that reduction by dissolving metals of steroid polyene systems through intermediate carbanions invariably affords the thermodynamically more stable product (W. S. Johnson *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 2275); similarly, Barton (Chemical Society Symposium, Manchester, 1954) found that 5-chlorocholestane on reduction with lithium in liquid ammonia gives cholestane in quantitative yield, whilst 5 : 6α-dibromocoprostane (Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066) gives cholestane, accompanied by cholest-5-ene but unaccompanied by coprostane. Thus, protonation or carboxylation affords the more thermodynamically stable arrangement at the asymmetric centre(s).

In regard to reaction (*b*), Cardwell, Cornforth, Duff, Holtermann, and Robinson (*J.*, 1953, 361) have suggested that reactions of lithium aluminium hydride, aluminium hydride, alkyl-lithiums, and alkylaluminiums with olefins and carbonyl groups proceed by electrophilic attack of aluminium on carbon or oxygen rather than by nucleophilic attack of hydrogen or alkyl on carbon, on the ground that covalent unions rather than preliminary electrovalent connections must be determinative. It seems highly probable that the reaction of alkylmagnesium halides with carbon dioxide may proceed by an analogous mechanism; Swain *et al.* (*J. Amer. Chem. Soc.*, 1947, **69**, 2306; 1950, **72**, 518) have shown by kinetic studies that, in the reaction of alkylmagnesium halides and alkyl-lithiums with cyano- or carbonyl groups, the rate-determining stage is an intramolecular rearrangement of a complex. The formation of such a complex will be favoured stereochemically by the

* We are grateful to a Referee for emphasising this point.

† The atomic dipole for a tetrahedral carbon orbital is ~2 D, which suggests that the average separation of charge may be of the order of 2 Å, a value which may be compared with the C–H bond length 1·09 Å (cf. Coulson, " Valence," Oxford Univ. Press, 1952, p. 208).

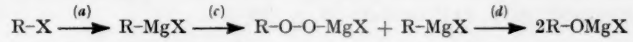
approximately rectangular configuration of the bonds from oxygen to carbon and oxygen to magnesium :



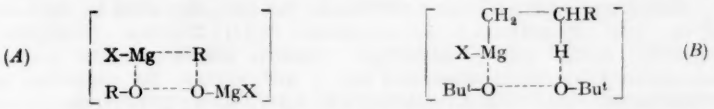
and, since the rearrangement is of S_Ni type, will occur with preservation of configuration.

We suggest that cholestanyl (V) and *epi*cholestanyl bromide (VII) on treatment with magnesium initially furnish the cholestan-3β-yl and cholestan-3α-yl anions; these at once undergo inter-conversion by passage through a planar form [sp^2-hybridisation with two *p*-orbitals each containing a single electron, and isoelectronic with the analogous form in NH_3 or NR_3 (cf. Linnett and Poë, *Trans. Faraday Soc.*, 1951, **47**, 1033)] to give exclusively the more stable cholestan-3β-yl anion (lone pair, equatorial), which by carboxylation yields only cholestane-3β-carboxylic acid [VI (CO_2H, equatorial)]. For cholesteryl (II) and *epi*cholesteryl bromide, it might be expected that the epimeric cholest-5-en-3β-yl and cholest-5-en-3α-yl anions would be formed initially and undergo equilibration to give exclusively the former (lone pair, equatorial), since apart from the greater thermodynamic stability of the equatorial conformation, the molecular geometry here will give rise to powerful repulsive forces between an unshared electron pair at $C_{(3)}$ and the π-electron cloud of the 5 : 6-double bond. It is consistent that cholesteryl bromide (II) by Grignard carboxylation gives only cholest-5-ene-3β-carboxylic acid [I (CO_2H, equatorial)], but *epi*cholesteryl bromide affords a single acid, which differs from cholest-5-ene-3α-carboxylic, and is provisionally termed cholest-5-ene-2ξ-carboxylic acid (cf. Shoppee, *Chem. and Ind.*, 1954, 759).

The mechanism of Grignard oxygenation appears to involve three stages :



since Walling and Buckler (*J. Amer. Chem. Soc.*, 1953, **75**, 4372) have isolated alkyl hydroperoxides formed in stage (*c*) in high yield, and have shown that treatment of alkylperoxymagnesium halide with additional Grignard reagent in stage (*d*) gives alcohols in high yield (personal communication). The stereochemical course of these reactions is obscure but in cyclic systems appears always to lead to racemisation with production of pairs of epimeric alcohols. We have not attempted to isolate the steroid hydroperoxide(s), but from the ultimate production of *epi*cholesterol (III) and cholesterol (IV), and of *epi*cholestanol (VIII) and cholestanol (IX) as described above, we infer that the racemisation process probably occurs in stage (*c*) and may be connected with the electronic structure of the oxygen molecule, because for stage (*d*) we postulate a four-centre transition state of S_Ni type (*A*) leading to retention of configuration in both the residues R. Campbell, Burney, and Jacobs



(*J. Amer. Chem. Soc.*, 1950, **72**, 2735) in a discussion of the reaction of di-*tert.*-butyl peroxide with Grignard reagents other than methylmagnesium halides have, however, proposed a six-centre transition state involving hydrogen bonding (*B*).

Experimental

For general directions see *J.*, 1954, 3178.

Cholesterol and epi*Cholesterol.*—A solution of cholesteryl bromide (1·17 g.), in ether (20 c.c.) was added to a solution of methylmagnesium iodide prepared from magnesium (0·25 g.), during 5 hr. During a total reflux period of 22 hr. a further quantity of methyl iodide (0·5 c.c.) in ether (5 c.c.) was added. Oxygen was then passed into the solution at 0° for 2 hr.; ice-cold 2*N*-sulphuric acid was added and the product extracted with ether. Washing, drying, and removal of solvent gave a product, which was chromatographed on a column of aluminium oxide (30 g.) prepared in pentane. Use of pentane (300 c.c.) as eluant furnished a mixture of

3β : 3β-dicholesteryl, other hydrocarbons, and unchanged cholesteryl bromide (630 mg.), whilst ether (200 c.c.) gave a mixture of alcohols (350 mg.) which was rechromatographed. Benzene–pentane (1 : 4; 6 × 30 c.c.) gave an oil (31 mg.), but use of benzene (6 × 30 c.c.) gave a solid (162 mg.), which was crystallised from methanol and had m. p. and mixed m. p. with authentic *epi*cholesterol 141°. Further elution with ether–benzene (1 : 1; 4 × 30 c.c.) gave a solid (166 mg.), which was crystallised from methanol to give cholesterol, m. p. and mixed m. p. 146—147°.

Cholestanol and epi*Cholestanol.*—(*a*) To a solution of methylmagnesium iodide prepared from magnesium (0·25 g.), ether (10 c.c.), and methyl iodide (0·1 c.c.) was added a solution of pure cholestan-3α-yl bromide (Roberts, Shoppee, and Stephenson, *loc. cit.*) (1 g.) in ether (10 c.c.). A further quantity of methyl iodide (0·4 c.c.) was added during the first 6 hr. of the total reflux period of 25 hr. The solution was then oxygenated at 0° during 4·5 hr. and the product isolated as in the previous experiment. Some ether-insoluble 3β : 3β-dicholestanyl (81 mg.) was removed, and the residue chromatographed on a column of aluminium oxide (24 g.) prepared in pentane. Use of pentane (3 × 80 c.c.) furnished a solid (651 mg.) consisting mainly of unchanged cholestan-3α-yl bromide; benzene–pentane (1 : 1, 3 × 80 c.c.) gave a solid (48 mg.) which, was crystallised from methanol, had m. p. 188°, and was identical with authentic *epi*cholestanol and characterised as the acetate, m. p. 96°. Further elution with benzene (80 c.c.) and with ether (80 c.c.) gave a solid (53 mg.) which, crystallised from methanol, had m. p. and mixed m. p. with cholestanol 144°, and was characterised as the acetate, m. p. 108°.

(*b*) A reaction was carried out on a similar scale and under similar conditions but with pure cholestan-3β-yl bromide (Roberts, Shoppee, and Stephenson, *loc. cit.*). The product was chromatographed on a column of aluminium oxide (24 g.). Use of pentane (4 × 80 c.c.) gave an oil (495 mg.), and benzene–pentane (1 : 4) again gave an oil (2 mg.); benzene–pentane (1 : 1; 3 × 80 c.c.) furnished a solid (108 mg.), which was crystallised from methanol and identified as *epi*cholestanol, m. p. 188° (acetate, m. p. 96°). Further elution with benzene (80 c.c.) and ether (80 c.c.) gave a solid (112 mg.), which was crystallised from methanol and identified as cholestanol, m. p. 144° (acetate, m. p. 109°).

One of us (G. R.) acknowledges the support of the Department of Scientific and Industrial Research.

UNIVERSITY OF WALES, UNIVERSITY COLLEGE OF SWANSEA. [*Received, June 12th,* 1954.]

---

*Steroids. Part VIII.** 3 : 5-cyclo*Ergosta*-7 : 9(11) : 22-*trien*-6β-*ol* (i-*Dehydroergosterol*).

By R. W. REES and C. W. SHOPPEE.

[Reprint Order No. 5393.]

Dehydroergosteryl toluene-*p*-sulphonate has been converted by methanolysis into 6β-methoxy-3 : 5-*cyclo*ergosta-7 : 9(11) : 22-triene [*i*-dehydroergosteryl methyl ether]. Hydrolysis similarly affords the free alcohol accompanied by dehydroergosterol and a hydrocarbon, the properties of which suggest that it is 3 : 5-*cyclo*ergosta-6 : 8(14) : 9(11) : 22-tetraene.

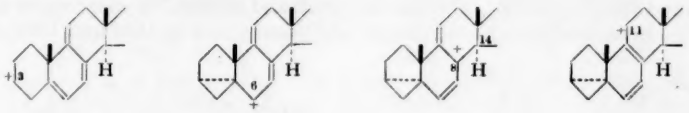
3 : 5-*cyclo*Ergosta-7 : 9(11) : 22-trien-6β-ol [*i*-dehydroergosterol], on treatment with mineral acid at 15°, reverts to dehydroergosterol; attempts to cause its acetate and *p*-nitrobenzoate to undergo anionotropic rearrangement to a 3 : 5-*cyclo*ergosta-6 : 8 : 22-trien-11ξ-ol were unsuccessful.

THE hormones of the adrenal cortex, *e.g.*, corticosterone, cortisone, and cortisol, are characterised by the presence of a substituent oxygen atom at $C_{(11)}$. One route for the partial synthesis of these compounds from naturally occurring steroids devoid of substituents in ring C involves the oxidation of steroid 7 : 9(11)-dienes with sodium dichromate dihydrate, perbenzoic, permonophthalic, performic, or peracetic acid; a second route involves merisation of a steroid 5 : 7 : 9(11)-triene to the 6 : 8(14) : 9(11)-triene, peroxidation, and hydrogenolysis of the 11 : 14-peroxide. It seemed possible that a third route could involve anionotropic rearrangement under appropriate conditions of a suitably 6-sub-

* Part VII, *J.*, 1954, 958.

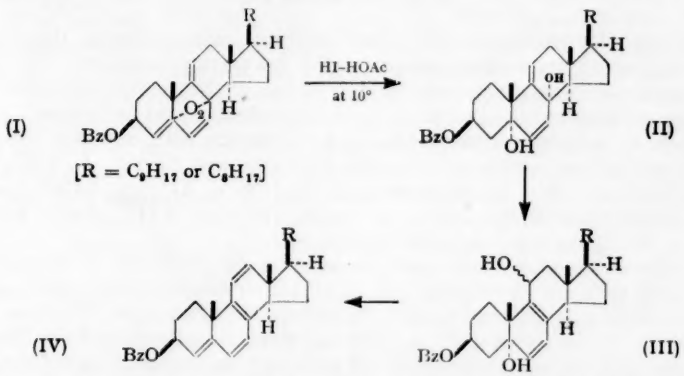
stituted steroid 7 : 9(11)-diene to yield an 11-substituted steroid 6 : 8-diene, or that electromeric extension of the 3 : 5-*cyclo*steroid rearrangement * might lead directly to such a compound.

Analogy with cholesterol (Shoppee and Summers, *J.*, 1952, 3361) suggests that application of the 3 : 5-*cyclo*steroid rearrangement to dehydroergosterol should furnish a set of mesomeric carbonium ions (*A*, *B*, *C*, *D*). In the carbonium ion (*B*) there is no adjacent hydrogen atom available for expulsion as a proton, and the sole path of depolarisation is combination with an external anion, *e.g.*, OH^-, at $C_{(6)}$ to yield a 3 : 5-*cyclo*ergosta-7 : 9(11) : 22-trien-6-ol. In the ions (*A*), (*C*), and (*D*), depolarisation can be achieved by co-ordination of an external anion, *e.g.*, OH^-, at $C_{(3)}$, $C_{(8)}$, or $C_{(11)}$, to give in the last case a 3 : 5-*cyclo*ergosta-6 : 8 : 22-trien-11-ol, or by ejection of a proton from $C_{(4)}$, $C_{(14)}$, or $C_{(12)}$, respectively, to give an unsaturated hydrocarbon.



(*A*) (*B*) (*C*) (*D*)

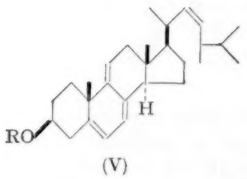
These considerations receive support from the recently reported conversion of the benzoates (I) of dehydroergosterol 5α : 8α-peroxide and of bisdehydrocholesterol 5α : 8α-peroxide, on treatment with hydriodic–acetic acid at 10° by way of labile intermediate 5α : 8α-diols (II) and 5α : 11ξ-diols (III), into ergosta-4 : 6 : 8 : 11 : 22-pentaen-3β-yl benzoate and cholesta-4 : 6 : 8 : 11-tetraen-3β-yl benzoate (IV) respectively (Feit, *Ber.*, 1953, **86**, 1252).



Dehydroergosteryl toluene-*p*-sulphonate (V; R = *p*-$C_6H_4Me{\cdot}SO_2$) is extremely unstable but by methanolysis in the presence of potassium acetate affords a 70% yield of a methyl ether, m. p. 53—54°, $[\alpha]_D$ +137°, $\lambda_{max.}$ 248 mμ, log ε 4·1, isomeric with dehydroergosteryl methyl ether (V; R = Me), m. p. 106°, $[\alpha]_D$ +166°, $\lambda_{max.}$ 324 mμ, log ε 4·0 (Heilbron and Simpson, *J.*, 1932, 268); we regard our ether as 3 : 5-*cyclo*ergosta-7 : 9(11) : 22-trien-6β-yl methyl ether (*i*-dehydroergosteryl methyl ether) (VI; R = Me), the β-configuration at $C_{(6)}$ being assigned by analogy with 3 : 5-*cyclo*-cholestan-6β-yl methyl ether (Shoppee and Summers, *loc. cit.*). The ultra-violet absorption characteristics are in good agreement with the values observed for cholest-7 : 9(11)-dien-3β-yl acetate, $\lambda_{max.}$ 245, 243 mμ, log ε 4·1, 4·15 (Dannenberg, *Abh. preuss. Akad. Wiss.*, 1939, **21**, 3; Dorfman, *Chem. Reviews*, 1953, **53**, 47; Fieser and Herz, *J. Amer. Chem. Soc.*, 1953, **75**, 121), and for methyl 3α-acetoxychola-

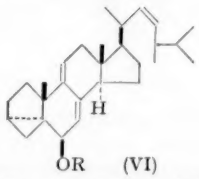
* An investigation of the application of the 3 : 5-*cyclo*steroid rearrangement to ergosterol was abandoned when it was learnt from Professor L. F. Fieser at the Symposium on Steroids at the American Chemical Society Meeting, New York, in September 1951, that such work was already proceeding at Harvard University.

7 : 9(11)-dienoate, $\lambda_{max.}$ 244·5 mμ, log ε 4·23 (Fieser, Huang, and Babcock, *ibid.*, p. 116), and with the value $\lambda_{max.}$ 244 mμ calculated by the method devised by Woodward (*ibid.*, 1942, **64**, 72) and extended by Fieser and Fieser ("Natural Products related to Phenanthrene," 3rd Edn., Reinhold, N.Y., 1949). They appear to exclude the structures 3 : 5-*cyclo*ergosta-6 : 9(11) : 22-trien-8ξ-yl methyl ether, derived from the cation (*C*), and 3 : 5-*cyclo*ergosta-6 : 8 : 22-trien-11ξ-yl methyl ether derived from the cation (*D*); the position of the ultra-violet absorption maximum in Δ⁶-3 : 5-*cyclo*steroids indicates some degree of hyperconjugation (Klotz, *ibid.*, 1944, **66**, 88), producing a bathochromic shift of ~15 mμ (Karrer and Asmis, *Helv. Chim. Acta*, 1952, **35**, 1926; Fieser, Rosen, and Fieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5397), so that for these structures the expected approximate values of $\lambda_{max.}$ are 210 and 290 mμ. The infra-red absorption spectrum strongly supports the structure (VI; R = Me); a 2% solution in carbon disulphide shows maxima at 1088 (ether link), at 968 (*trans*-CHR=CHR; Δ^{22}), at 848 and 810 (CR_2=CHR; $\Delta^{9(11)}$), and at 1020 and 892 cm.$^{-1}$ (*cyclo*propane ring), whilst a 2% solution in carbon tetrachloride shows additional peaks at 1384 and 1370 cm.$^{-1}$ (*gem*-



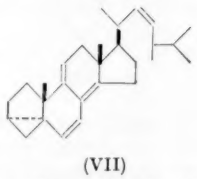
(V)

R = H; m. p. 146°, $[\alpha]_D$ +150°, $\lambda_{max.}$ 324 mμ, log ε 4·0
R = Ac; m. p. 146°, $[\alpha]_D$ +204°
R = Me; m. p. 106°, $[\alpha]_D$ +166°



(VI)

R = H; m. p. 47°, $[\alpha]_D$ +139°, $\lambda_{max.}$ 247 mμ, log ε 4·2
R = Ac; m. p. 38°, $[\alpha]_D$ +112°
R = Me; m. p. 53°, $[\alpha]_D$ +137°, $\lambda_{max.}$ 248 mμ, log ε 4·1



(VII)

M. p. 102°, $[\alpha]_D$ +81°, $\lambda_{max.}$ 252 mμ, log ε 4·2

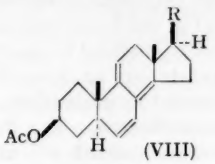
dimethyl group). By treatment with dilute sulphuric acid in dioxan, the methyl ether (VI; R = Me) undergoes rearrangement to give dehydroergosterol (V; R = H); with hydrogen chloride or bromide in acetic acid, solutions of the methyl ether (VI; R = Me) became green, turning to blue, but no crystalline products could be isolated.

Hydrolysis of dehydroergosteryl toluene-*p*-sulphonate with aqueous acetone in the presence of potassium acetate (cf. Beynon, Heilbron, and Spring, *J.*, 1937, 406) gives dehydroergosterol (V; R = H), an isomeric alcohol, m. p. 47°, $[\alpha]_D$ +139°, $\lambda_{max.}$ 247 mμ, log ε 4·1, characterised as the acetate, m. p. 36—38°, $[\alpha]_D$ +112°, and a hydrocarbon, $C_{28}H_{40}$, m. p. 102°, $[\alpha]_D$ +81°, $\lambda_{max.}$ 252 mμ, log ε 4·2.

The position of the ultra-violet absorption maximum at 247 mμ in the new alcohol is again consistent with a 3 : 5-*cyclo*steroid-7 : 9(11) : 22-triene structure (calc. $\lambda_{max.}$ 244 mμ), derived from the cation (*B*), and appears to exclude the alternative structures 3 : 5-*cyclo*ergosta-6 : 9(11) : 22-trien-8ξ-ol (calc. $\lambda_{max.}$ 210 mμ) and 3 : 5-*cyclo*ergosta-6 : 8 : 22-trien-11ξ-ol (calc. $\lambda_{max.}$ 290 mμ) derived from cations (*C*) and (*D*); we therefore regard the compound as 3 : 5-*cyclo*ergosta-7 : 9(11) : 22-trien-6β-ol (*i*-dehydroergosterol) (VI; R = H). It was stable to hot 2N-methanolic potassium hydroxide, but was rearranged by dilute sulphuric acid in dioxan to dehydroergosterol (V; R = H). With hydrogen chloride or hydrogen bromide in acetic acid a deep green colour was produced and an impure substance, m. p. 100—110°, $\lambda_{max.}$ 212 mμ, containing bromine (?3β : 8ξ-dibromoergosta-6 : 9(11) : 22-triene) was isolated.

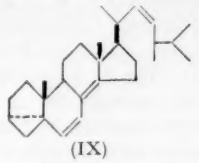
The hydrocarbon, $C_{28}H_{40}$, cannot be ergosta-3 : 5 : 7 : 9(11) : 22-pentaene, which might have been produced by internal depolarisation of the carbonium ion (*A*), because the observed absorption maximum at 252 mμ is much too low for such a structure [calc. $\lambda_{max.}$ 353 mμ; obs. for the enol acetate of ergosta-4 : 7 : 9(11) : 22-tetraen-3-one, $\lambda_{max.}$ 355 mμ, log ε 4·24 (Heilbron, Kennedy, Spring, and Swain, *J.*, 1938, 869)]; the alternative 2 : 4 : 6 : 9(11) : 22-pentaene [calc. $\lambda_{max.}$ 308 mμ; obs. for cholesta-2 : 4 : 6-triene, $\lambda_{max.}$ 305 mμ, log ε 4·15 (Schmutz, Schaltegger, and Sanz, *Helv. Chim. Acta*, 1951, **34**, 1111)] and -2 : 4 : 6 : 8 : 22-pentaene (calc. $\lambda_{max.}$ 343 mμ) structures appear likewise to be excluded. Internal depolarisation of the cation (*C*) would furnish 3 : 5-*cyclo*ergosta-6 : 8(14) : 9(11) : 22-

tetraene (VII). The absorption maximum for this cross-conjugated system cannot be calculated, but must lie near the values 243 mμ (log ε 4·08) for cholesta-6 : 8(14) : 9(11)-trien-3β-yl acetate * (VIII; R = C_8H_{17}) observed by Windaus *et al.* (*Annalen*, 1938, **534**, 22; 1942, **552**, 135, 142), and 233 mμ (log ε 4·25) for ergosta-6 : 8(14) : 9(11) : 22-tetraen-3β-yl acetate * (VIII; R = C_9H_{17}) observed by Laubach *et al.* (*J. Amer. Chem. Soc.*, 1953, **75**, 1514). Addition of the increment for hyperconjugation of the *cyclo*propane ring (15 mμ) suggests a value for $\lambda_{max.}$ 248—258 mμ, which corresponds fairly well with the observed maximum at 252 mμ, and is consistent with the maximum reported for 3 : 5-*cyclo*ergosta-



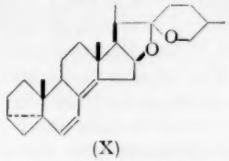
(VIII)

R = C_8H_{17}; m. p. 102°, $\lambda_{max.}$ 243 mμ, log ε 4·08
R = C_9H_{17}; m. p. 151°, $[\alpha]_D$ −94°, $\lambda_{max.}$ 233 mμ, log ε 4·25



(IX)

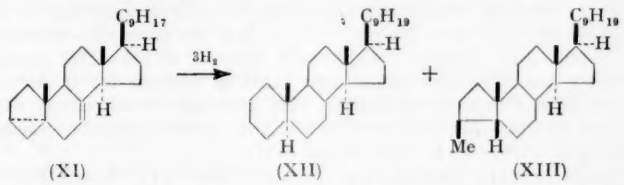
M. p. 102°, $[\alpha]_D$ +92°, $\lambda_{max.}$ 260 mμ, log ε 4·4



(X)

M. p. 172°, $[\alpha]_D$ +108°, $\lambda_{max.}$ 256 mμ, log ε 4·3

6 : 8(14) : 22-triene (IX; $\lambda_{max.}$ 260 mμ) by Fieser, Rosen, and Fieser (*ibid.*, 1952, **74**, 5397) and for 3 : 5-*cyclo*-22a-spirosta-6 : 8(14)-diene (X; $\lambda_{max.}$ 256 mμ) by Djerassi (personal communication). Internal depolarisation of the cation (*D*) would furnish 3 : 5-*cyclo*ergosta-6 : 8 : 11 : 22-tetraene, the absorption maximum of which should lie between that of cholesta-6 : 8 : 11-triene (calc. $\lambda_{max.}$ 303 mμ) and that of cholesta-4 : 6 : 8 : 11-tetraen-3β-ol [calc. $\lambda_{max.}$ 343 mμ; obs. $\lambda_{max.}$ 355 mμ, log ε 4·13 (Windaus *et al.*, *loc. cit.*), of its benzoate (IV; R = C_8H_{17}) [obs. $\lambda_{max.}$ 355 mμ, log ε 4·19 (Feit, *loc. cit.*)], and of ergosta-4 : 6 : 8 : 11 : 22-pentaen-3β-yl benzoate (IV; R = C_9H_{17}) [obs. $\lambda_{max.}$ 355; log ε 4·23 (Feit, *loc. cit.*)]. We therefore regard the hydrocarbon, $C_{28}H_{40}$, as 3 : 5-*cyclo*ergosta-6 : 8(14) : 9(11) : 22-tetraene (VII), despite its anomalous reaction with perbenzoic acid. Although all types of steroid nuclear double bond react with perbenzoic acid, the hydrocarbon on treatment with an excess of perbenzoic acid absorbed only 2 instead of 4 equivalents of oxygen. Difficulty was also encountered in catalytic hydrogenation of the hydrocarbon; hydrogenation with platinum–acetic acid–dioxan stopped completely after 3 mols. had been adsorbed, and the product was still unsaturated towards tetranitromethane. Further hydrogenation with platinum–acetic acid at 70—100°/150 atm. furnished material still unsaturated to tetranitromethane, from which crystalline fractions could not be obtained.



(XI) (XII) (XIII)

Since hydrogenation of 3 : 5-*cyclo*ergosta-7 : 22-diene (XI) gives a mixture of a little ergostane (XII), m. p. 84°, with much 3β-methyl-A-nor-5β-ergostane (XIII), m. p. 77° (Karrer and Asmis, *Helv. Chim. Acta*, 1952, **35**, 1926), and since steroid 8(14)-double bonds resist hydrogenation—*e.g.*, Bladon *et al.* (*J.*, 1951, 2402), prepared 3β-acetoxyergost-8(14)-ene [" α "-ergostenyl acetate] from 3β-acetoxyergosta-7 : 22-diene by hydrogenation with platinum–acetic acid–ether at 100°/100 atm.—we consider that our product is probably a mixture of the hydrocarbon (XIII) and ergost-8(14)-ene, m. p. 80° (Heilbron, Spring, and Webster, *J.*, 1932, 1705).

Whilst the infra-red spectra of the above non-crystalline fractions showed only a general likeness to that of authentic ergost-8(14)-ene (Bladon *et al.*, *loc. cit.*), nevertheless,

* These compounds exhibit a secondary maximum at $\lambda_{max.}$ 285 mμ, log ε 3·96 and at $\lambda_{max.}$ 288 mμ, log ε 3·82 respectively.

the hydrocarbon structure (VII) is strongly supported by the infra-red absorption spectrum; a 2% solution of (VII) in carbon disulphide shows maxima at 968 [*trans*-CHR=CHR; Δ^{22}], at 824 and 810 [CR_2=CHR; $\Delta^{9(11)}$], at 764 and 742 [*cis*-CHR=CHR; Δ^{6}], and at 1020 and 884 cm.$^{-1}$ (*cyclo*propane ring), whilst a 2% solution in carbon tetrachloride shows additional peaks at 1382 and 1365 cm.$^{-1}$ (*gem*-dimethyl group).

Mobility in anionotropic systems is promoted (*a*) by catalysis by acids, (*b*) by media of high dielectric constant, and (*c*) by the increasing stability as an anion of the migrating group (OH < OAc < ·O·CO·C_6H_4·NO_2-*p* < Hal) (Burton and Ingold, *J.*, 1928, **904**, 1650). The conversion of the 3 : 5-*cyclo*-6β-ol (VI; R = H) into an 11ξ-hydroxy-steroid by catalysis by mineral acid was precluded because the conjugate acid of the former has been shown to revert to dehydroergosterol (V; R = H); we were therefore confined to an examination of the effect of factors (*b*) and (*c*). The 3 : 5-*cyclo*-6β-yl acetate was unchanged when heated with acetic anhydride (dielectric constant 20) or with methyl cyanide (dielectric constant 39); the 3 : 5-*cyclo*-6β-yl *p*-nitrobenzoate was likewise unaffected. The 3 : 5-*cyclo*-6β-yl *p*-nitrobenzoate was also heated with pyridine (dielectric constant 12) at 140° in the presence of added pyridinium *p*-nitrobenzoate (cf. Burton, *J.*, 1934, 1268), but was recovered unaltered. It seems unlikely that conditions suitable for the conversion of a 3 : 5-*cyclo*-steroid-7 : 9(11)-diene-6-ol into an 11ξ-hydroxy-steroid can be devised, but we are investigating the possible anionotropic conversion of other steroid-7 : 9(11)-dien-6-ols into 11ξ-hydroxy-steroids.

Experimental

For general experimental directions, see preceding paper. $[\alpha]_D$ are in $CHCl_3$ unless otherwise stated, whilst ultra-violet absorption spectra were determined in EtOH on a Unicam SP.500 spectrometer with corrected scale and infra-red absorption spectra in CS_2 on a Perkin–Elmer double-beam instrument,

Dehydroergosteryl Toluene-p-*sulphonate*.—Dehydroergosterol (20 g.; dried by azeotropic distillation with benzene), dissolved in dry pyridine (20 c.c.), was treated with a solution of purified toluene-*p*-sulphonyl chloride (20 g.; dried at 20°/0·01 mm.) in dry pyridine (50 c.c.) in an atmosphere of dry nitrogen. The solution was kept at 30—35° for 10 min., left overnight at 10°, and poured into a saturated solution of sodium hydrogen carbonate. After 1 hr., the precipitate was filtered off, washed with water and methanol, and recrystallised from acetone to give *dehydroergosteryl toluene*-p-*sulphonate* (19 g.), m. p. 130° (decomp. with production of a red colour), $[\alpha]_D^{20}$ +170° (*c*, 2·80) * [Found (after drying at 15°/0·02 mm. for 4 hr.): C, 76·9; H, 8·9. $C_{35}H_{48}O_3S$ requires C, 76·6, H, 8·8%] (cf. Buisman and Westerhof, *Rec. Trav. chim.*, 1952, **71**, 925). A similar product was obtained by the procedure described by Karrer and Asmis (*Helv. Chim. Acta*, 1952, **35**, 1926). The toluene-*p*-sulphonate is a white crystalline solid, which rapidly becomes yellow and after some months decomposes to a black tar. It could be chromatographed on neutral aluminium oxide in pentane, elution with pentane giving a specimen, m. p. 140—143° (decomp.), whose m. p. dropped to 130—135° during a few days at room temperature; use of alkaline aluminium oxide in pentane led to decomposition since elution with pentane and benzene–pentane (1 : 19) gave oils, which slowly solidified, and by crystallisation from acetone–methanol gave material, m. p. 100°, probably consisting essentially of 3 : 5-*cyclo*ergosta-6 : 8(14) : 9(11) : 22-tetraene (VII).

3 : 5-cyclo*Ergosta*-7 : 9(11) : 22-*trien*-6β-*yl Methyl Ether* (VI; R = OMe).—Dehydroergosteryl toluene-*p*-sulphonate [m. p. 130° (decomp.); 4 g.] was heated with anhydrous potassium acetate (12 g.; freshly fused) in dry methanol (800 c.c.) for 4 hr. Methanol (400 c.c.) was removed by distillation and then by evaporation at 35°/10 mm.; after addition of water, the product was extracted with ether, and the extract washed with water, dried, and evaporated. The resultant oil (3·3 g.) was chromatographed on aluminium oxide (100 g.) in pentane. Elution with pentane (5 × 300 c.c.) yielded material (total 2·30 g.) which crystallised; by recrystallisation from methanol this gave 3 : 5-cyclo*ergosta*-7 : 9(11) : 22-*trien*-3β-*yl methyl ether*, m. p.

* It may be useful to record that cholesteryl toluene-*p*-sulphonate has $[\alpha]_D^{15}$ −39° (*c*, 2·20), and to note that 7-dehydrocholesteryl toluene-*p*-sulphonate, m. p. 105° (decomp.) (B, K), has $[\alpha]_D$ −38° (K), whilst ergosteryl toluene-*p*-sulphonate, m. p. 114° (B), 116° (F), 105° (K) (decomp.), has $[\alpha]_D$ −119° (!) (B), −45° (F), −46° (K) [B = Buisman and Westerhof (*loc. cit.*); F = Fieser, Rosen, and Fieser (*J. Amer. Chem. Soc.*, 1952, **74**, 5397); K = Karrer and Asmis (*loc. cit.*)]. The increments in $[M]_D$ for conversion of −OH ⟶ O·SO_2·C_6H_4Me-*p* thus appear to increase from zero for cholesterol to +250° for $\Delta^{5:7}$-sterols and to +350° for a $\Delta^{5:7:9(11)}$-sterol.

53—54°, $[\alpha]_D^{20}$ +137° (*c*, 1·97), $\lambda_{max.}$ 248 mμ, log ε 4·1 [Found (after drying at 15°/0·01 mm. for 18 hr.): C, 85·0; H, 10·8; OMe, 8·1. $C_{29}H_{44}O$ requires C, 85·2; H, 10·85; OMe, 7·6%]; the compound gave a positive Rosenheim test (red ⟶ intense green), and a positive Tortelli–Jaffé test (intense green). Elution with benzene yielded yellow solid material (228 mg.), giving by crystallisation from acetone an unidentified substance, m. p. 174—175° with decomp. at 180°, $[\alpha]_D$ −7° (*c*, 1·07), $\lambda_{max.}$ 226 mμ, log ε 4·2 (if M = 400) [Found (after drying at 15°/0·01 mm. for 18 hr.): C, 75·65; H, 9·4; OMe, 3·4%].

The methyl ether (270 mg.), dissolved in 90% dioxan (50 c.c.), was treated with 2N-sulphuric acid (0·35 c.c.) at 15° for 15 hr. The product, isolated in the usual way, was chromatographed on aluminium oxide; elution with pentane yielded some oil, but elution with benzene and ether–benzene (1 : 1) furnished dehydroergosterol, m. p. 144°, mixed m. p. 144—146°.

The methyl ether (700 mg.) was treated with acetic acid (100 c.c.) containing 48% hydrobromic acid (10 c.c.) at 15°; the solution at once became dark green, and after being kept overnight contained a yellow precipitate, which was filtered off (m. p. 92—93°). This material, which contained bromine, could not be crystallised satisfactorily from any solvent. The filtrate furnished a brown oil, which was dissolved in benzene–pentane and filtered through aluminium oxide; the resulting yellow oil did not crystallise. It contained bromine, and was refluxed with zinc dust in acetic acid for 1 hr.; chromatography of the reduction product gave only oils (eluted with pentane).

3: 5-cyclo*Ergosta*-7:9(11):22-*trien*-6β-*ol* (VI; R = H) *and* **3**:5-cyclo*Ergosta*-6:9(11):8(14):22-*tetraene* (VII).—Dehydroergosteryl toluene-*p*-sulphonate (4·36 g.) was heated with potassium acetate (10 g.) in aqueous acetone (2 : 1; 375 c.c.) for 6 hr. The product, isolated in the usual way after removal of acetone at 10 mm., was an oil (3·48 g.) which soon crystallised and was chromatographed on aluminium oxide (100 g.) in pentane. Elution with pentane (300 c.c.) yielded crystals (160 mg.) which, recrystallised from acetone, gave **3**: 5-cyclo*ergosta*-6 : 9(11) : 8(14) : 22-*tetraene* (VII) as needles, m. p. 102°, $[\alpha]_D^{20}$ +81° (*c*, 2·00), $\lambda_{max.}$ 252 mμ, log ε 4·2 [Found (after drying at 60°/0·03 mm. for 4 hr.): C, 88·8; H, 10·8. $C_{28}H_{40}$ requires C, 89·3; H, 10·7%]; the hydrocarbon gave a deep orange colour with tetranitromethane, and positive Rosenheim (green) and Tortelli–Jaffé tests. Further elution with pentane (4 × 300 c.c.) gave oils (total 1·41 g.), which slowly solidified and by recrystallisation from acetone–methanol furnished **3**: 5-cyclo*ergosta*-7 : 9(11) : 22-*trien*-6β-*ol* (VI; R = H), m. p. 46—47°, $[\alpha]_D^{15}$ +139° (*c*, 1·107), $\lambda_{max.}$ 247 mμ, log ε 4·2 [Found (after drying at 15°/0·02 mm. for 20 hr.): C, 85·0; H, 10·6. $C_{28}H_{42}O$ requires C, 85·2; H, 10·7%], giving positive Rosenheim (green) and Tortelli–Jaffé tests; it was characterised by preparation (acetic anhydride–pyridine at 15° for 15 hr.) of the *acetate*, which crystallised on cooling in the presence of acetone–methanol, and, recrystallised with some difficulty from methanol at −80°, had m. p. 36—38°, $[\alpha]_D^{15}$ +112° (*c*, 0·61) [Found (after drying at 20°/0·01 mm. for 4 hr.): C, 82·8; H, 10·2. $C_{30}H_{44}O_2$ requires C, 82·5; H, 10·15%], and the p-*nitrobenzoate*, needles (from methanol), m. p. 82—85° [Found: N, 2·7. $C_{35}H_{45}O_4N$ requires N, 2·6%]. Further elution with pentane (2 × 300 c.c.) yielded uncrystallisable material (128 mg.), but use of benzene–pentane mixtures gave dehydroergosterol, m. p. and mixed m. p. 146°, $[\alpha]_D^{15}$ +155° (*c*, 1·40), after recrystallisation from acetone; elution with benzene and with ether also gave dehydroergosterol (total, 1·80 g.). From some experiments, carried out under conditions apparently identical with those described, only **3**: 5-*cyclo*ergosta-6 : 9(11) : 8(14) : 22-tetraene (VII) and dehydroergosterol could be isolated; this inconsistency is to be attributed to variation in the quality of dehydroergosteryl toluene *p*-sulphonate produced in different preparations.

3: 5-*cyclo*Ergosta-7 : 9(11) : 22-trien-6β-ol (m. p. 46°; 115 mg.) was refluxed with methanolic 2N-potassium hydroxide for 2·5 hr.; cooling, addition of a few drops of water, saturation with carbon dioxide, and vacuum-evaporation gave unchanged material (95 mg.), m. p. 44° after crystallisation from acetone–methanol. The **3**: 5-*cyclo*trien-6β-ol (110 mg.), dissolved in 90% aqueous dioxan (15 c.c.), was treated with 2N-sulphuric acid (0·13 c.c.) at 15° for 24 hr.; the product (95 mg.), isolated in the usual way, was chromatographed on a long column of aluminium oxide (6 g.) prepared in pentane. Elution with pentane (3 × 10 c.c.) gave starting material (8 mg.), m. p. 45°, after crystallisation from acetone–methanol; elution with benzene–pentane mixtures furnished no material, but use of benzene and ether–benzene (1 : 1) gave dehydroergosterol (57 mg.), m. p. 144° after recrystallisation from methanol. The **3**: 5-*cyclo*trien-6β-ol (50 mg.) was dissolved in ether and shaken with 2N-hydrochloric acid but no colour developed and the starting material was recovered; when the **3**: 5-*cyclo*trien-6β-ol (110 mg.) was dissolved in acetic acid (10 c.c.) and treated with concentrated hydrochloric acid (1 c.c.) at 15°, the solution immediately became dark green, but after 24 hr. no crystalline product could be isolated by chromatography. When the

3 : 5-*cyclo*trien-6β-ol (102 mg.) was treated in acetic acid (10 c.c.) with 48% hydrobromic acid (1 c.c.) at 15°, the solution at once became dark green. Next morning, the product was isolated in the usual way as a brown oil (105 mg.) which solidified partially on being rubbed with pentane. The material, dissolved in benzene–pentane (1 : 4), was filtered through a column of aluminium oxide (5 g.), to yield a coloured solid which could not be satisfactorily purified by crystallisation or chromatography. The product, m. p. 100—110°, $\lambda_{max.}$ 212 mμ, contained bromine and gave a negative Rosenheim test.

3 : 5-*cyclo*Ergosta-6 : 9(11) : 8(14) : 22-tetraene (VII) (44·5 mg.) was treated with a chloroform solution (6·0 c.c.) of perbenzoic acid (23 mg./c.c.) for 3 days at 20°; at the end of this period the concentration in a blank experiment was unchanged, and the perbenzoic acid consumed was 33·5 mg. (2·05 mols.). In another experiment with the hydrocarbon (110 mg.) at 0°, the perbenzoic acid consumed was 57 mg. (1·41 mols.).

3 : 5-*cyclo*Ergosta-6 : 9(11) : 8(14) : 22-tetraene (45 mg.), dissolved in pure dry carbon tetrachloride (3 c.c.), by titration with a solution of bromine in carbon tetrachloride (17·2 mg./c.c.) required 5·50 c.c. (9·8 atom-equiv. of Br) to give a faint yellow colour; at 20° the solution rapidly darkened, to give finally a green amorphous precipitate.

3 : 5-*cyclo*Ergosta-6 : 9(11) : 8(14) : 22-tetraene (89 mg.), dissolved in pure dioxan (5 c.c.) and acetic acid (50 c.c.), was hydrogenated with pre-reduced platinum oxide (42 mg.) at 19°. Hydrogenation ceased after 50 min. and no further absorption occurred during 40 min. (16·4 c.c., 2·92 mols.); the product (101 mg.), obtained from the filtered solution by evaporation at 20°/0·1 mm. for 5 hr., could not be caused to crystallise and gave a yellow colour with tetranitromethane–chloroform. Further hydrogenation was attempted with platinum oxide in acetic acid at 70—100°/150 atm. in a Cook autoclave for 5 hr.; the cooled solution was filtered, the filtrate evaporated in a vacuum, and the residue dissolved in purified ethyl acetate. The solution was washed with water, treated with charcoal, dried, filtered through a layer of magnesium sulphate, and evaporated. The residue (84 mg.) still gave a yellow colour with tetranitromethane–chloroform; chromatography on aluminium oxide (3 g.) and elution with pentane and with hexane gave 4 fractions (5 mg.; 42 mg.; 28 mg.; 5 mg.), of which Nos. 2 and 3 failed to crystallise on inoculation with ergost-8(14)-ene although giving a yellow colour with tetranitromethane–chloroform.

Attempted Anionotropic Rearrangement.—3 : 5-*cyclo*Ergosta-7 : 9(11) : 22-trien-6β-yl acetate (VI; R = Ac) (50 mg.) was heated with acetic anhydride (5 c.c.) in a small ampoule at 100° for 5 hr.; the product, obtained by vacuum-evaporation and crystallisation from methanol at −80°, was unchanged (m. p. 35—38°). A similar experiment with methyl cyanide also failed.

3 : 5-*cyclo*Ergosta-7 : 9(11) : 22-trien-6β-yl *p*-nitrobenzoate (60 mg.) was dissolved in pyridine (3 c.c.) containing *p*-nitrobenzoic acid (30 mg.), and the solution heated in a small bomb-tube at 140° for 12 hr. The cooled, dark red solution was evaporated in a vacuum, and the product extracted with ether; the ethereal solution was washed with 2N-hydrochloric acid, water, and sodium hydrogen carbonate solution, dried, and evaporated. The residue by recrystallisation from methanol gave unchanged starting material (26 mg.), m. p. 82—85°. No other crystalline product could be isolated.

One of us (R. W. R.) acknowledges the award of a University Postgraduate Studentship. We are grateful to Glaxo Laboratories Ltd. for the infra-red spectra and for the high-pressure hydrogenation; we thank Professor P. Karrer, Zürich, for a specimen of ergostane, and Professor E. R. H. Jones, Manchester, for a specimen of ergost-8(14)-ene.

University of Wales, University College of Swansea. [*Received, May 17th,* 1954.]

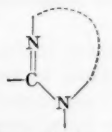
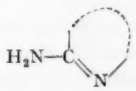
Cyclic Amidines. Part I. Derivatives of Phenhomazine (Dibenzo[b, f]-1 : 5-diazocine).

By F. C. Cooper and M. W. Partridge.

[Reprint Order No. 5387.]

o-Cyanoanilinium toluene-*p*-sulphonate, on being heated, affords 6 : 12-diaminophenhomazine (III; X = Y = NH_2) and tricycloquinazoline (IV). Dianthranilide can be prepared by interaction of methyl anthranilate, a nitrile, and sodium. A generalised interpretation of this reaction, applicable to a number of analogous reactions, is suggested. The light-absorption characteristics of a number of phenhomazine derivatives are recorded.

The amidine group may form a fragment of a heterocyclic ring either as a chain of three atoms (I) or as a chain of two atoms with one nitrogen as a ring substituent (II). A variety of methods has been applied to the synthesis of both types of cyclic amidine. However, the reactions leading to the formation of semicyclic amidines are essentially of two types despite the wide range of heterocyclic rings which have been obtained by these methods. In the first type, ring formation has involved, at an appropriate stage, the addition of the group :NH to the group ·C:N; for example, in compounds containing one heterocyclic nitrogen atom, this addition has been exploited in the synthesis of pyrrolidines (Best and Thorpe, *J.*, 1909, **95**, 1506), pyridines (von Meyer, *J. pr. Chem.*, 1914, **90**, 29), and indoles (Pschorr and Hoppe, *Ber.*, 1910, **43**, 2543). In the second type of synthesis, the exocyclic nitrogen is introduced into the preformed heterocyclic ring either by an addition to the ammono-aldehyde system ·N:CH· (*e.g.*, Tschitschibabin and Zeide, *J. Russ. Phys. Chem. Soc.*, 1914, **46**, 1216) or by replacement of halogen in a cyclic analogue of an imidoyl halide ·N:CHal· (*e.g.*, den Hertog and Wibaut, *Rec. Trav. chim.*, 1932, **51**, 381).

(I)   (II)

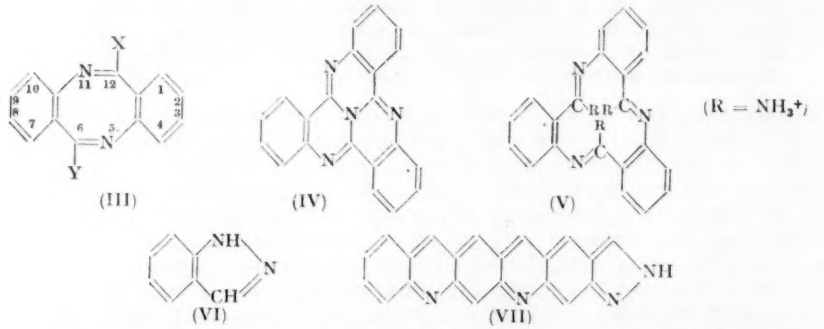
This series of communications deals with the application to the synthesis of semicyclic and cyclic amidines of the methods recently developed for the preparation of open-chain amidines, especially those involving the addition of :NH to ·C:N (Oxley and Short, *J.*, 1946, 147; Cooper and Partridge, *J.*, 1953, 255).

A simple example of the addition of :NH to ·C:N to form a semicyclic amidine is provided by the polymerisation of a salt of *o*-cyanoaniline. The rigidity with which the two *ortho*-substituents are held renders this reaction capable of affording a product containing an 8-membered ring, namely, 6 : 12-diaminophenhomazine (III; X = Y = NH_2). By analogy of this reaction with the anhydrisation of salicylic acid (Baker, Ollis, and Zealley, *J.*, 1951, 201), the simultaneous formation of products resulting from a higher degree of polymerisation would be expected.

In agreement with these speculations, we find that the isolable products from the material formed when *o*-cyanoanilinium toluene-*p*-sulphonate is heated for a short time are 6 : 12-diaminophenhomazine monotoluene-*p*-sulphonate (III; X = NH_2; Y = NH_3^+)$C_7H_7O_3S^-$ or a tautomeride) and tricycloquinazoline (IV). Tricycloquinazoline is apparently formed in this reaction by condensation of the trimer (V) of the *o*-cyanoanilinium cation. A compound isomeric with tricycloquinazoline formed when indazole (VI) is heated with copper powder was tentatively assigned the constitution (VII) (Jacobson and Huber, *Ber.*, 1908, **41**, 660). We find that the compound obtained in this way is identical in melting point and light-absorption characteristics with tricycloquinazoline prepared by heating *o*-aminobenzaldehyde with ammonium chloride (Kozak and Kalmus, *Bull. Acad. polonaise*, 1933, **10**, *A*, 532). Since indazole and *o*-cyanoaniline are isomeric, it is not unexpected that they could both yield tricycloquinazoline under appropriate conditions.

The constitution of the 6 : 12-diaminophenhomazine prepared from *o*-cyanoanilinium toluene-*p*-sulphonate was confirmed by comparison as the base, dihydrochloride, monohydrochloride, monotoluene-*p*-sulphonate, and picrate with specimens prepared by heating 6 : 12-dichlorophenhomazine (III; X = Y = Cl) (Schroeter, *Ber.*, 1919, **52**, 2224) with methanolic ammonia at 150°.

Derivatives of phenhomazine have hitherto received little attention. Contrary to the statement of Morton, "The Chemistry of Heterocyclic Compounds," McGraw-Hill, New York,



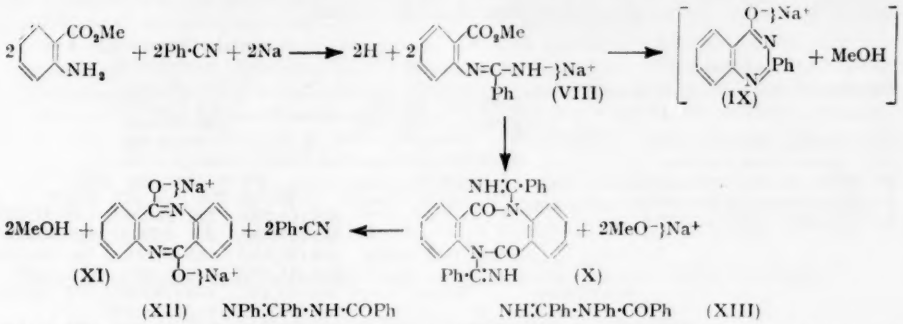
1946, p. 271, phenhomazine itself is not formed when *o*-aminobenzaldehyde is kept at pH 3 (cf. Schöpf and Lehmann, *Annalen*, 1932, **497**, 7; Bamberger, *Ber.*, 1927, **60**, 314). The most readily accessible derivative of phenhomazine, namely, dianthranilide (III; X = Y = OH or its tautomeride), was prepared by hydrolysis of the product of acetolysis of an *NN'*-diarylsulphonyldianthranilide which is itself formed when an *o*-arylsulphonamidobenzoyl chloride undergoes condensation in pyridine (Schroeter and Eisleb, *Annalen*, 1909, **367**, 101; Schroeter, *loc. cit.*).

In an attempt to extend an open-chain amidine synthesis (Cooper and Partridge, *loc. cit.*) to the preparation of 2-amino-4-hydroxyquinolines, we examined the reaction of acetonitrile with methyl anthranilate in the presence of " powdered " sodium in boiling benzene. The main product formed was dianthranilide. The same compound can be obtained more simply and in better yield by the use of benzonitrile instead of acetonitrile. Dianthranilide prepared in this way afforded *NN'*-dimethyl (Schroeter and Eisleb, *loc. cit.*) and *NN'*-diethyl derivatives by treatment with the appropriate dialkyl sulphate in the presence of alkali. The corresponding ethers (III; X = Y = OMe and X = Y = OEt) were obtained by boiling 6 : 12-dichlorophenhomazine with alcoholic solutions of the respective alkoxides.

We suggest that the foregoing reactions resulting in the production of dianthranilide may be interpreted as in the annexed scheme. Evidence in support of the formation of a substituted amidine (VIII) in the first stage of the reaction was provided by the isolation of 4-hydroxy-2-phenylquinazoline (cf. IX) as a by-product. Collateral evidence for the condensation of the sodioamidine (VIII) to yield *NN'*-dibenzimidoyldianthranilide (X) was obtained by demonstrating that *N*-phenylbenzamidine is benzoylated by boiling together its sodio-derivative and ethyl benzoate in benzene; the main product isolated was *N*-benzoyl-*N'*-phenylbenzamidine (XII). The formation of benzoic acid, dibenzoylamine, and benzanilide, isolated as by-products, can be accounted for in several ways. It is known that on benzoylation at a low temperature *N*-phenylbenzamidine affords *N*-benzoyl-*N*-phenylbenzamidine (XIII) (Wheeler, Johnson, and McFarland, *J. Amer. Chem. Soc.*, 1903, **25**, 787) which rearranges with great facility to the more stable *N*-benzoyl-*N'*-phenylbenzamidine (XII). The constitution of the main product of the benzoylation of *N*-phenylbenzamidine with ethyl benzoate is therefore in accordance with expectation. An analogous rearrangement in the case of *NN'*-dibenzimidoyldianthranilide appears to be extremely unlikely since this would involve fission of the 8-membered ring and formation of a 12-membered ring.

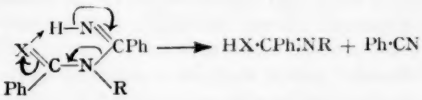
The postulated decomposition of *NN'*-dibenzimidoyldianthranilide (X) to dianthranilide

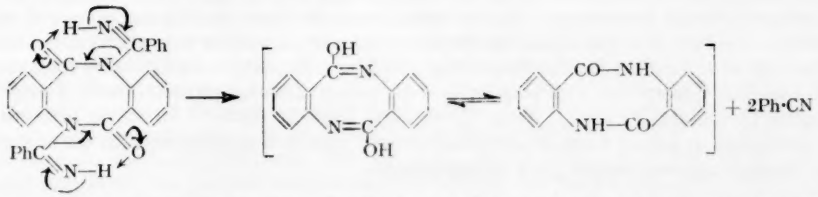
(cf. XI) and benzonitrile is similar to that observed in a number of open-chain analogues having the structure NH:CPh·NR·CPh:X; *N*-benzoyl-*N*-phenylbenzamidine (R = Ph, X = O; see below), 2 : 4-diphenyl- (R = H, X = NH) (Peak, *J.*, 1952, 215), 1 : 2 : 4-triphenyl- (R = H; X = NPh), and 1 : 2 : 3 : 4-tetraphenyl-1 : 3 : 5-triazapenta-1 : 4-diene (R = Ph;



(XII) NPh:CPh·NH·COPh NH:CPh·NPh·COPh (XIII)

X = NPh) (Cooper, Partridge, and Short, *J.*, 1951, 391) all afford benzonitrile and a second product varying according to the nature of R and X. It is probable that the decomposition is initiated by the formation of a hydrogen bond which governs the subsequent electron drifts :





The process then becomes consistent not only with the foregoing decompositions but also with the fission of diamidides and triamidides with acids (Cooper, Partridge, and Short, *loc. cit.*) and with the formation of cyanides by the decomposition of imidic esters (Wislicenus and Goldschmidt, *Ber.*, 1900, **33**, 1467), of amidines (Oxley, Partridge, and Short, *J.*, 1948, 303), of imidoyl sulphonates (Oxley, Partridge, Robson, and Short, *J.*, 1946, 763; Oxley, Peak, and Short, *J.*, 1948, 1618), and of cyanamides by the decomposition of *O*-arylsulphonylureas (Oxley, Partridge, Peak, and Short, *Chem. and Ind.*, 1949, 419; Partridge and Turner, *J. Pharm. Pharmacol.*, 1953, **5**, 103).

The suggestion that the reaction is simply a base-catalysed condensation of methyl anthranilate cannot be sustained since when this compound was boiled with " powdered " sodium in benzene, sodium ethoxide in benzene, or sodium ethoxide in ethanol, the maximum yield of dianthranilide was 4%. It may appear from the suggested interpretation of the reaction leading to the formation of dianthranilide that not more than a catalytic quantity of benzonitrile would be required. However, benzonitrile is consumed in reactions of this kind not only in the formation of the quinazolone (cf. IX) but also by reduction to benzene and a number of other products (Cooper and Partridge, *loc. cit.*; Anker and Cook, *J.*, 1941, 323).

The light-absorption characteristics of a number of phenhomazine derivatives are summarised in the Table. It is clear from the absence of absorption at long wave-lengths that the eight-membered ring in dianthranilide and its dialkyl ethers is not in cyclic conjugation with the aromatic rings and in this respect these compounds resemble 1 : 2 : 5 : 6-

dibenzo*cyclo*octatetraene (Fieser and Pechet, *J. Amer. Chem. Soc.*, 1946, **68**, 2577). Indeed, it is apparent that even the simple co-planar conjugated structure of the chromophoric systems of ethyl benzimidoate, benzamide, or *NN'*-dimethylbenzamide, which absorb at 225—228 mμ (Ley and Specker, *Ber.*, 1939, **72**, 192), cannot be assumed. The partial chromophore of dianthranilide in neutral or in acid solution appears to be similar to that of its *NN'*-dialkyl derivatives rather than its dialkyl ethers.

Compound		Solvent	Light absorption (mμ; ε in parentheses)
Dianthranilide		EtOH	214 (28,500)
,,		N/10-HCl–EtOH	214 (28,800)
,,		N/10-NaOH–EtOH	230 (20,400)
NN'-Dimethyldianthranilide		EtOH	212 (24,800)
NN'-Diethyldianthranilide		EtOH	213 (20,900)
6 : 12-Dimethoxyphenhomazine		EtOH	208 (8,700); 251 (950)
6 : 12-Diethoxyphenhomazine		EtOH	209 (13,700); *ca. 260* (2,200)
6 : 12-Diaminophenhomazine		EtOH	*206* (10,700); 223 (29,100); 235 (31,100) *262* (17,500); 301 (9,000); 330 (7,900)
,,		N/100-HCl–EtOH	208 (39,600); 242 (30,500); 280 (25,200) 314 (10,700); *330* (7,300); 415 (9,400)
,,	monohydrochloride	Water	206 (33,400); 234 (29,500); *275* (15,300) 315 (9,000); *ca. 360* (4,200)
,,	dihydrochloride	Water	205 (34,200); 230 (28,900); 274 (17,300) 313 (9,100); 360 (4,600)
,,	,,	4N-HCl	210 (25,900); 261 (33,600); 322 (9,700)

Figures in italics denote inflexions. The solvent EtOH refers to ethanol (95%).

No simple interpretation of the bright yellow colour of the monohydrochloride of 6 : 12-diaminophenhomazine is apparent. Some similarities to 9-aminophenanthridine might be expected, but this forms a colourless solution in acid (Morgan and Walls, *J.*, 1932, 2225). The colour of the singly charged cation may be a manifestation of charge resonance of forms having the proton donated to the ring nitrogen (cf. Craig and Short, *J.*, 1945, 419) and strained planar structures. On the other hand, the band at 415 mμ, observed with a solution of the base in N/100-ethanolic hydrogen chloride, is similar in position and intensity to that reported for 5-aminoacridine (Craig and Short, *loc. cit.*). In alcoholic solution, the base exhibits absorption characteristics resembling 2-aminoquinoline and 1-amino*iso*quinoline (Steck and Ewing, *J. Amer. Chem. Soc.*, 1948, **70**, 3397). In strong acid solution the absorption at longer wave-lengths disappears; this is in agreement with the suggestion that charge resonance would then be suppressed.

Experimental

o-*Cyanoanilinium Toluene*-p-*sulphonate*.—Interaction of *o*-chloronitrobenzene (52·5 g., 0·33 mole), cuprous cyanide (32·9 g., 0·37 mole), and pyridine (29·0 g., 0·37 mole) at 160° for 4 hr., then at 180° for 1 hr., and addition of the melt to hydrochloric acid (350 ml.) afforded crude *o*-cyanonitrobenzene (32·0 g., 65%), m. p. 103—106°, raised to 107·5—108·5° after crystallisation from acetic acid (Bogert and Hand, *J. Amer. Chem. Soc.*, 1902, **24**, 1031, record m. p. 109·5°). *o*-Cyanoaniline (Bogert and Hand, *loc. cit.*) (15 g.) was warmed with toluene-*p*-sulphonic acid (25 g.) in water (40 ml.) until homogeneous; on cooling, the solution deposited o-*cyanoanilinium toluene*-p-*sulphonate* (27·7 g., 94%) as prisms, m. p. 170—171°, unchanged by crystallisation from *iso*propyl alcohol (Found: C, 57·8; H, 4·75. $C_{14}H_{14}O_3N_2S$ requires C, 57·9; H, 4·85%). The *picrate*, red prisms from water, had m. p. 109—110° (Found: C, 45·0; H, 2·6. $C_{13}H_9O_7N_5$ requires C, 45·0; H, 2·6%).

Action of Heat on o-*Cyanoanilinium Toluene*-p-*sulphonate*.—When *o*-cyanoanilinium toluene-*p*-sulphonate (20 g.) was heated in a refluxing nitrobenzene vapour-bath for 15 min., the temperature of the melt rose to 230° after 5 min., and then rapidly dropped to 210°, while the clear liquid became pasty. The cooled melt was powdered and extracted successively with hot water (4 × 150 ml.) and hot 1·5N-hydrochloric acid (250 ml.). The orange residue (2·4 g.), m. p. 317—320°, was crystallised from xylene and gave 1·9 g. (26%) of tricycloquinazoline as fluffy yellow needles, m. p. 322—323°, not depressed by an authentic specimen (see below) (Found: C, 79·1; H, 3·6; N, 17·7. Calc. for $C_{21}H_{12}N_4$: C, 78·75; H, 3·75; N, 17·5%). When kept for 10 days the aqueous extract deposited an orange solid (2·2 g.), which was fractionally crystallised from ethanol and afforded 6 : 12-*diaminophenhomazine monotoluene*-p-*sulphonate* (0·25 g., 2%) as

small orange needles, m. p. 280—282° (Found : C, 61·5; H, 4·9; N, 13·3; S, 7·9. $C_{21}H_{20}O_3N_4S$ requires C, 61·75; H, 4·95; N, 13·7; S, 7·85%); it was characterised by conversion into the monopicrate (see below), which had m. p. 225—227° and mixed m. p. 226—228°. Another toluene-*p*-sulphonate (0·95 g.), m. p. 228—229°, separated during this fractional crystallisation but was not identified. The aqueous filtrate and acid extract were combined and made alkaline with ammonia, and the resulting precipitate (4·0 g.) was crystallised from 4N-hydrochloric acid, affording **6** : 12-diaminophenhomazine dihydrochloride monohydrate (2·55 g., 18%), m. p. and mixed m. p. 285—287° (decomp.). Samples of the base, monohydrochloride, and monopicrate made from this dihydrochloride had m. p. and mixed m. p. identical with those described below.

Tricycloquinazoline.—(i) *o*-Aminobenzaldehyde (4 g.) and ammonium chloride (10 g.), treated according to the directions of Kozak and Kalmus (*loc. cit.*), gave 0·6 g. (17%) of tricycloquinazoline as fluffy yellow needles, m. p. 322—323° after crystallisation from toluene. Kozak and Kalmus state that this compound melts at 308—310°.

(ii) When indazole (1 g.) and copper powder (1 g.) were heated together as described by Jacobson and Huber (*loc. cit.*), 0·15 g. (17%) of tricycloquinazoline, m. p. and mixed m. p. 322—323°, was obtained. Jacobson and Huber record m. p. 318—319° for a compound made in this way.

Absorption spectra of the compound made in various ways are recorded in the Table.

Light absorption of tricycloquinazoline in chloroform.

From *o*-cyanoaniline	$\lambda_{max.}$	252	284	296	310	378	400	424	452 mμ
	$\varepsilon_{max.}$	40,900	23,500	32,600	29,200	23,800	23,000	8200	2600
From *o*-aminobenzaldehyde	$\lambda_{max.}$	252	284	296	310	378	400	424	450 mμ
	$\varepsilon_{max.}$	42,300	23,100	31,600	28,400	23,000	22,400	8000	2500
From indazole	$\lambda_{max.}$	252	284	296	310	380	400	424	450 mμ
	$\varepsilon_{max.}$	45,100	25,400	34,500	31,300	25,100	24,500	8700	2700

Dianthranilide.—(i) When methyl anthranilate (45·4 g., 0·3 mole), powdered sodium (13·8 g., 0·6 g.-atom), and acetonitrile (24·6 g., 0·6 mole) were mixed in dry benzene (170 ml.) at room temperature, the initial exothermic reaction caused the mixture to boil vigorously and much light brown solid separated; the mixture was then refluxed for 24 hr. The cooled mixture was shaken with water (150 ml.) and with 2N-sodium hydroxide (70 ml.), and the mixed aqueous solutions, after charcoal treatment, were added to excess of hydrochloric acid, affording crude dianthranilide (17·1 g., 48%), m. p. 320—327°, which, after crystallisation from ethanol, had m. p. 335—337°, not depressed by an authentic specimen (see below) (Found : C, 70·6; H, 3·8; N, 12·1. Calc. for $C_{14}H_{10}O_2N_2$: C, 70·6; H, 4·25; N, 11·75%). With periods of refluxing of 0, 0·5, and 21 hr., the yields of crude dianthranilide were 30, 31, and 40% respectively. With twice the above proportion of acetonitrile and with 3·5 hours' refluxing, the yield was 38%. With double the proportion of both acetonitrile and of sodium and with 20 hours' refluxing, the yield was 44%; after removal of the dianthranilide the mother-liquors were neutralised with ammonia and the precipitated solid was crystallised from benzene, affording 0·4 g. of an amphoteric compound, possibly 2-*anthraniloylmethyl*-4-*hydroxyquinazoline*, as small, pale yellow needles, m. p. 176—177° [Found : C, 68·5; H, 4·65; N, 15·3%; *M* (Rast), 268. $C_{16}H_{13}O_2N_3$ requires C, 68·8; H, 4·7; N, 15·05%; *M*, 279].

(ii) There was no reaction when methyl anthranilate (22·7 g., 0·15 mole), powdered sodium (6·9 g., 0·3 g.-atom), and benzonitrile (30·9 g., 0·3 mole) were mixed in benzene (70 ml.) at room temperature. After the vigorous exothermic reaction which was initiated by warming had subsided, the mixture was refluxed for 2 hr. and cooled. The resulting suspension was extracted with water (70 ml.) and then with 2N-sodium hydroxide (40 ml.); this extract, after treatment with charcoal, afforded, on the addition of hydrochloric acid, dianthranilide (8·8 g., 49%), m. p. 332—335°, raised by crystallisation from ethanol to 335—337°, not depressed by an authentic specimen. Neutralisation of the filtrate with ammonia gave a solid (1·9 g.), m. p. 220—228°, which, when crystallised from ethanol (charcoal), gave 4-hydroxy-2-phenylquinazoline (1·5 g., 4·5%), as needles, m. p. 235—236° (Bischler and Lang, *Ber.*, 1895, **28**, 279, give m. p. 235—236°) (Found : C, 75·5; H, 4·7. Calc. for $C_{14}H_{10}ON_2$: C, 75·65; H, 4·55%). Distillation of the extracted benzene solution afforded benzonitrile (7·25 g., 0·07 mole), b. p. 74—76°/16 mm., n_D^{19} 1·5289.

Repetition of the foregoing experiment but with the proportion of benzonitrile reduced to 0·23 mole and with refluxing for 3 and 4 hr. gave 55 and 56% respectively of dianthranilide.

(iii) Interaction of methyl anthranilate (0·1 mole) and sodium (0·1 g.-atom) in refluxing

benzene for 8 hr. afforded a 4% yield of dianthranilide : similarly, interaction in boiling ethanol for 12 hr. gave a 3% yield. No dianthranilide was isolated when methyl anthranilate (0·1 mole), sodium (0·3 g.-atom), and ethanol (0·1 mole) were boiled together for 22 hr. in benzene.

(iv) Dianthranilide, prepared by Schroeter and Eisleb's method (*loc. cit.*), had m. p. 335—337° ; Schroeter and Eisleb record m. p. about 330°. *NN'*-Ditoluene-*p*-sulphonyldianthranilide, an intermediate in this synthesis, had m. p. 252—253° which rose on storage to 271—272°. Schroeter and Eisleb give m. p. 240° for this compound (Found : C, 61·7 ; H, 4·1. Calc. for $C_{28}H_{22}O_6N_2S_2$: C, 61·5 ; H, 4·05%).

6 : 12-*Dichlorophenhomazine*.—Made by Schroeter's method (*loc. cit.*), this had m. p. 219—220° : (Found : C, 61·2 ; H, 3·25. Calc. for $C_{14}H_8N_2Cl_2$: C, 61·15 ; H, 2·95%). Schroeter gives m. p. 220°.

NN'-Dimethyldianthranilide.—This, prepared by Schroeter and Eisleb's method (*loc. cit.*), had m. p. 205—207° : Schroeter and Eisleb record m. p. 207°.

NN'-Diethyldianthranilide was prepared in 60% yield by shaking together dianthranilide (1·0 g.) and diethyl sulphate (1·3 g.) in 0·5N-sodium hydroxide (17 ml.) frequently during 6 hr. It crystallised from benzene–light petroleum (b. p. 80—100°) as prisms, m. p. 192—193° (Found : C, 73·4 ; H, 6·3. $C_{18}H_{18}O_2N_2$ requires C, 73·5 ; H, 6·15%).

6 : 12-*Dimethoxyphenhomazine*.—**6** : 12-Dichlorophenhomazine (2·0 g.) was added to sodium (0·35 g.) dissolved in methanol (100 ml.), and the solution was refluxed for 26 hr. The residue obtained by evaporating the solution to dryness was stirred with water, and the resultant solid (1·8 g., 93%), m. p. 161—162°, afforded **6** : 12-*dimethoxyphenhomazine* as prisms, m. p. 161—162°, on crystallisation from light petroleum (b. p. 100—120°) (Found : C, 72·5 ; H, 5·45. $C_{16}H_{14}O_2N_2$ requires C, 72·15 ; H, 5·3%). This compound was soluble in concentrated hydrochloric acid but was precipitated by the addition of water. The *monopicrate*, made by interaction of the base and picric acid in benzene, crystallised as slender yellow prisms, m. p. 144—155°, from benzene–light petroleum (b. p. 60—80°) (Found : C, 53·5 ; H, 3·55 ; N, 14·2. $C_{22}H_{17}O_9N_5$ requires C, 53·3 ; H, 3·45 ; N, 14·15%). Attempts to crystallise the picrate from methanol, ethanol, or *iso*propyl alcohol yielded the base.

6 : 12-*Diethoxyphenhomazine*, formed as above in 98% yield from **6** : 12-dichlorophenhomazine, sodium, and ethanol, crystallised as prisms, m. p. 146—147°, from light petroleum (b. p. 100—120°) (Found : C, 73·9 ; H, 6·25. $C_{18}H_{18}O_2N_2$ requires C, 73·5 ; H, 6·15%).

6 : 12-*Diaminophenhomazine*.—A suspension of finely powdered **6** : 12-dichlorophenhomazine (5 g.) in 14% w/w methanolic ammonia (200 g.) was heated in a rotary autoclave at 120—150° for 6 hr. The resultant solution was evaporated to dryness, the residue dissolved by warming with 50 ml. of 1·5N-hydrochloric acid, and the solution filtered from a trace of insoluble matter. 20 ml. of this solution were added to excess of aqueous ammonia and afforded **6** : 12-*diaminophenhomazine* (1·7 g., 39%), which crystallised from aqueous ethanol as small colourless cubes, m. p. 127—128° (Found : C, 71·1 ; H, 5·25 ; N, 23·4. $C_{14}H_{12}N_4$ requires C, 71·2 ; H, 5·1 ; N, 23·7%). The base crystallised from benzene as very small, pale yellow rods, m. p. 92—93° with effervescence, containing solvent of crystallisation which was lost on prolonged storage (Found : C, 76·3 ; H, 5·75 ; N, 18·3. $C_{14}H_{12}N_4$, C_6H_6 requires C, 76·4 ; H, 5·8 ; N, 17·8%). The remaining 30 ml. of acid solution, on cooling, deposited **6** : 12-*diaminophenhomazine dihydrochloride monohydrate* (3·2 g., 54%) as pale yellow needles, m. p. 283—286° (decomp.), changed to 285—287° (decomp.) by crystallisation from 4N-hydrochloric acid [Found : C, 51·2 ; H, 5·2 ; N, 16·8 ; Cl, 22·1 ; H_2O (Karl Fischer), 6·3. $C_{14}H_{12}N_4$,2HCl,H_2O requires C, 51·4 ; H, 4·95 ; N, 17·1 ; Cl, 21·65 ; H_2O, 5·5%]. When a solution of the dihydrochloride in hot water was cooled, slender orange needles of the *monohydrochloride* were deposited, having m. p. 283—287° (decomp.), unchanged by recrystallisation from water [Found : C, 61·6 ; H, 5·1 ; N, 20·4 ; Cl, 13·0 ; H_2O (Karl Fischer), Nil. $C_{14}H_{12}N_4$,HCl requires C, 61·65 ; H, 4·8 ; N, 20·55 ; Cl, 13·0%]. The *monopicrate*, prepared by interaction of the base and sodium picrate in aqueous lactic acid, crystallised from glacial acetic acid as solvated brownish-red needles, m. p. 227—228° (decomp.) when slowly heated from 120° but melting immediately with effervescence when inserted into a bath at 210° (Found : loss at 150°/vac., 10·2. Found, on dried material : C, 51·4 ; H, 3·35 ; N, 21·0. $C_{20}H_{15}O_7N_7$,$C_2H_4O_2$ requires $C_2H_4O_2$, 11·4. $C_{20}H_{15}O_7N_7$ requires C, 51·6 ; H, 3·25 ; N, 21·05%).

6 : 12-Dichlorophenhomazine failed to give any recognisable basic product when treated with ethanolic ammonia for 3 weeks at room temperature or with sodamide for 22 hr. in refluxing benzene : 42% and 80% respectively of starting material was recovered. No recognisable products were isolated when **6** : 12-dichlorophenhomazine was heated at 120—130° with ammonium carbonate in phenol or at 210° with urea.

Interaction of N-Phenylbenzamidine, Sodium, and Ethyl Benzoate.—To a suspension of sodio-*N*-phenylbenzamidine made by refluxing *N*-phenylbenzamidine (9·8 g., 0·05 mole) and sodium (1·15 g., 0·05 g.-atom) in dry benzene (150 ml.) for 24 hr. was added ethyl benzoate (7·5 g., 0·05 mole); the mixture was refluxed for a further 8 hr., during which nearly all the solid dissolved. The resulting mixture afforded benzoic acid (0·9 g.), dibenzoylamine (0·4 g.), and *N*-phenylbenzamidine (2·7 g.) by extraction first with water and then with acid; benzanilide (0·15 g.) and *N*-benzoyl-*N'*-phenylbenzamidine (3·4 g.) were isolated from the benzene-soluble products by fractional crystallisation from ethanol.

THE UNIVERSITY, NOTTINGHAM. [*Received, May 14th*, 1954.]

The Analysis of Inorganic Compounds by Paper Chromatography. Part VI. Further Studies on the Separation and Detection of Lanthanons.*

By F. H. POLLARD, J. F. W. MCOMIE, and H. M. STEVENS.

[Reprint Order No. 5200.]

Tests for distinguishing between lanthanon groups and certain individual lanthanons are given.

A number of substances were investigated for use in the preparation of complex-forming mobile phases and, of the latter, those consisting of 8-hydroxyquinoline in a *n*-butanol–water–acetic acid system yielded the best lanthanon separations. These appeared to depend on differences in ionic radii, with Y coming between Gd and Dy.

Factors affecting the percentage yield of "didymium" from a mixture with cerium have been investigated, and successful separations between members of the cerium group and between this group and Y are described.

Brief qualitative investigations suggested some resolution in two "heavy-earth" mixtures.

OUR previous work (Part V *) using 8-hydroxyquinoline (oxine) as a complexing and detecting agent has been extended. Antipyrine, *o*-aminophenol, and a number of substituted quinolines and pyridines have also been investigated as complex-forming reagents in the separation of lanthanons, but none of these compounds is as efficient as oxine. The movement of lanthanons in oxine-containing mobile phases probably depends on the stability of the "oxinates" in addition to their partition coefficients. Paper-strip experiments upon a number of binary mixtures have shown that in general the degree of resolution increases with the difference in the radii of the lanthanon ions. Yttrium is interpolated between Gd and Dy in the separations (see p. 3438).

The resolution of "didymium"–cerium mixtures on cellulose columns is very satisfactory if small loads are employed. These experiments suggest that in Part V (*loc. cit.*) the columns were too heavily loaded to permit of maximum resolution. The degree of separation is also diminished by increasing the Ce content of the mixture. If the loads are small good resolutions are obtained among lanthanons of the cerium group, and between this group and Y. With antipyrine as the complex-forming agent a good separation between La and Y has been obtained on a column, but resolutions among the metals of the cerium group are inferior to those when oxine is used. The resolutions of a La–Y mixture on paper strips using 8-hydroxyquinaldine or 3-hydroxypyridine as the complex-forming agent are as good as those obtained with antipyrine, but expense prohibited the use of these reagents on the column scale. Qualitative column experiments have indicated some resolution in mixtures containing (*a*) Y, Er, Tm, Yb, and Lu; (*b*) Y, Gd, Dy, Ho, and Er.

Individual lanthanons and lanthanon groups can be distinguished by using four spray-reagents [pyrogallol-4-carboxylic acid, ammonium purpurate (murexide), tetrahydroxy-

* Part V, *J.*, 1952, 4730.

flavonol (morin) and oxine] upon spots of the nitrates, in addition to the behaviour and R_F values of lanthanon spots on paper strips run in oxine-containing solvents.

Experimental

Preparation of Lanthanon Solutions.—Available lanthanon material consisted of: B.D.H. samples of yttrium nitrate, lanthanum nitrate, and cerous nitrate, and " Specpure " oxides of praseodymium (Pr_6O_{11}), neodymium, samarium, gadolinium, terbium, dysprosium, erbium, thulium, and lutecium. Ytterbium oxide was obtained from a sample of the acetate kindly given by Dr. J. K. Marsh.

Aqueous nitrate solutions were prepared by evaporating to dryness 2—3 mg. of the required oxide or nitrate with a few drops of 2N-nitric acid, and dissolving the residue in 0·25—0·5 ml. of water. The following binary mixtures were prepared similarly: La–Ce, La–Pr, La–Sm, La–Gd, La–Y, La–Dy, La–Yb, Ce–Nd, Ce–Sm, Ce–Y, Ce–Dy, Ce–Yb, Pr–Gd, Pr–Y, Pr–Dy, Pr–Yb, Sm–Gd, Sm–Y, Sm–Dy, Sm–Yb, Gd–Dy.

Reagents for Distinguishing between Lanthanons.—Dried lanthanon nitrate spots on strips of Whatman No. 1 paper were treated by spraying them with the following solutions, and examining them as indicated:

(1) 2% (w/v) Pyrogallol-4-carboxylic acid (" Py·CO_2H ") in 50% alcohol, followed by a saturated aqueous solution of sodium hydrogen carbonate; the strip was examined after being kept for a few minutes, or gently warmed. (2) Aqueous ammonium purpurate (" murexide ") solution; the strip was examined on exposure to ammonia. (3) 1% (approx.) (w/v) 8-Hydroxyquinoline (oxine) in 50% alcohol; the dried strip was examined over ammonia in ultra-violet light. (4) Tetrahydroxyflavonol (" morin ") in 50% alcohol; the dried strip was examined in ultra-violet light. The results are recorded in Table 1.

Table 1. (ff = brightly fluorescent, f = fluorescent, d = dark spot in ultra-violet light.)

Cation	(1) " Py·CO_2H "	(2) " Murexide "	(3) " Oxine "	(4) " Morin "
Y	Brown	Pinkish orange	* ff (yellow-green)	ff (green)
La	Bright purple	Bright violet	ff (green)	ff (green)
Ce^{3+}	Purple, turning brown	,,	d	d
Pr	Bright purple	,,	d	d
Nd	,,	,,	d	d
Sm	Dirty purple	Purplish pink	d	d
Gd	Purple brown	,,	* f (deep brown)	f (green)
Tb	Brown	Pink	d	d
Dy	,,	Orange-yellow	d	d
Er	,,	,,	d	d
Tm	,,	,,	d	d
Yb	,,	,,	d	d
Lu	,,	,,	* ff (yellow-green)	ff (green)

* Different colours are obtained if the cations are run on paper strips in an oxine-containing solvent (see Table 2).

With " Py·CO_2H " and " murexide " colours are readily produced with the lighter earths, but the response of the heavier earths is much poorer. The latter, being weaker bases, are presumably more easily precipitated under the alkaline conditions and so do not respond to the tests.

It is noteworthy that the lanthanons which fluoresce with " oxine " and " morin " are those which contain the most stable electronic groupings in their orbitals.

All four reagents have been found useful in detecting and distinguishing between lanthanons of the " light " and " heavy " groups on paper strips which have been run in eluants containing no powerful complex-forming substances (*e.g.*, oxine).

Preparation of Eluants.—Mixtures of the constituents for eluants (A)—(D) were warmed until a homogeneous solution was obtained; (E) and (F) were prepared as described.

(A) Water-saturated *n*-butanol (100 ml.), oxine (5 g.), acetic acid (10 ml.)
(B) ,, ,, (100 ml.), ,, (5 g.), ,, (14 ml.)
(C) ,, ,, (100 ml.), ,, (5 g.), ,, (20 ml.)
(D) ,, ,, (100 ml.), antipyrine (11 g.), ,, (10 ml.)
(E) *n*-Butanol (100 ml.), acetic acid (13 ml.), and water (30 ml.) were mixed; to 110 ml. of the mixture 5 g. of oxine were added (with warming to render the solution homogeneous).

(F) To a mixture of *n*-butanol (100 ml.) and water (30 ml.) ethanol was added until a homogeneous solution was obtained upon vigorous shaking. To 100 ml. of this mixture antipyrine (11 g.) and acetic acid (10 ml.) were added (with warming until homogeneous).

n-Butanol could be replaced by other alcohols, and mixtures of alcohols, which could contain 15% of water and which had similar (or slower) drip-rates compared with *n*-butanol from a capillary tube at constant head of liquid. Of such alcohols, *sec.*-butyl, *tert.*-butyl, or mixtures of (i) *n*-amyl (60 ml.) and *iso*propyl (40 ml.) or (ii) *n*-hexyl (70 ml.) and ethyl (30 ml.) were used to replace *n*-butyl alcohol in paper-strip experiments on La–Pr and La–Y mixtures. To prepare the eluant, 15 ml. of water, 5 g. of oxine (or 11 g. of antipyrine), and 10 (or 14) ml. of acetic acid were added to 85 ml. of the alcohol or alcohol mixture.

The following complex-forming agents gave inferior results to oxine when used in the *n*-butanol–acetic acid system for paper-strip experiments: (i) 8-Hydroxy-2-methylquinoline, (ii) 2-hydroxyquinoline, (iii) 2-hydroxypyridine, (iv) 3-hydroxypyridine, (v) 8-hydroxy-7-iodoquinoline-5-sulphonic acid, (vi) *o*-aminophenol. Partial resolution of a La–Y mixture occurred with (i) and (iv); (ii), (v), and (vi) would not dissolve sufficiently to give a 5% w/v solution.

Section A. Paper-strip Experiments.

Spots of the nitrate solutions were run individually upon acid-washed Whatman No. 1 paper strips in eluant (C). After drying, the strips were examined in daylight and ultra-violet light. The R_F values of the oxinate spots were calculated, and the behaviour of the spots in ultra-violet light noted (Table 2). To prevent backward tailing of the metals Sm to Lu a considerable concentration of acetic acid was necessary.

TABLE 2.

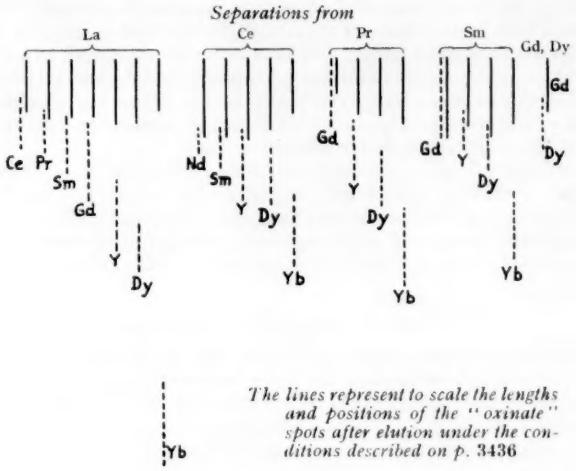
Lanthanon	Colour of oxide	R_F value of oxinate spot or most concentrated zone	Behaviour in U.V. light
Y	White *	0·47	f (golden)
La	,,	0·34	f (green)
Ce	Cream	0·40	d
Pr	Dark brown	0·40	d
Nd	Blue	0·43	d
Sm	Pale yellow	0·44	d
Gd	White	0·44	d
Tb	Dark brown	0·47	d
Dy	Yellowish	0·50	d
Er	Pink	≏0·50	d
Tm	White	0·66	d
Yb	,,	0·70	d
Lu	,,	0·59 to 0·76	f (golden-brown)

* B.D.H. yttrium nitrate yields a pale orange-brown oxide.

Notes on Table 2.—The R_F values follow, in general, the order of the increasing ionic radii and of decreasing basicity of the lanthanons. The oxinates of the more electrovalent lanthanons of the "light" group would be expected to be less stable than those of the "heavy" group. Consequently, the latter would tend to move to higher R_F values in the organic phase, while the former may tend to be adsorbed on to the paper as ions, giving low R_F values. The movement and separation of lanthanons is cut down by reducing the oxine content of butanol–acetic acid solvent systens, and the total exclusion of the complex-forming reagent causes practically no movement as the lanthanons are presumably adsorbed on to the paper in an ionic state. A similar phenomenon was noted when studying the movement of certain cations in solvent systems containing benzoylacetone (Elbeih, McOmie, and Pollard, *Discuss. Faraday Soc.*, 1949, **7**, 183). The stability of lanthanon "oxinates" may therefore be an important factor which operates in conjunction with a partition mechanism in these separations.

From the results of paper-strip runs upon the binary mixtures in eluant (E) it was observed that backward tailing was prevented by the presence of La. When this metal was not present such tailing could be eliminated by: (i) increasing the acetic acid content of the eluant (this was detrimental to separations between light earths), (ii) using dilute lanthanon solutions, (iii) dissolving the nitrates in the eluant instead of in water—this probably caused the formation of oxinates in solution before the strip run begins: hydrolysis, and the adsorption of cations by the cellulose were thereby prevented.

The Figure shows, diagrammatically, resolutions which were obtained by running aqueous nitrate spots of the binary lanthanon mixtures upon acid-washed Whatman No. 1 paper strips in eluant (E) for approximately 14 hr.



The lines represent to scale the lengths and positions of the "oxinate" spots after elution under the conditions described on p. 3436

Notes on the Figure—(i) Where one spot is formed (*e.g.*, with Pr, Gd) the colour of the oxide obtained by ashing various portions was used to indicate the distribution of cations within the spot. Thus Pr (dark brown ash) was found to concentrate at the rear, and Gd (white ash) at the front of the zone.

(ii) The greater the difference in the basicities, the more completely will a pair of lanthanons be resolved. Thus from the Figure it is seen that the degree of separation in the four series can be arranged as shown below. Differences in ionic radii are given in parentheses :

(*a*) La, Yb > La, Dy > La, Y > La, Gd > La, Sm > La, Pr > La, Ce
(0·22) (0·15) (0·16) * (0·11) (0·09) (0·06) (0·04)
(*b*) Ce, Yb > Ce, Dy > Ce, Y > Ce, Sm > Ce, Nd
(0·18) (0·11) (0·12) * (0·05) (0·03)
(*c*) Pr, Yb > Pr, Dy > Pr, Y > Pr, Gd
(0·16) (0·09) (0·10) * (0·05)
(*d*) Sm, Yb > Sm, Dy > Sm, Y > Sm, Gd
(0·13) (0·06) (0·07) * (0·02)

From the results marked * it is noted that the degree of separation of La, Pr, and Sm from Y is intermediate between that of the same metals from Gd and Dy. Y is also interpolated between Gd and Dy in Table 2, which suggests that its basicity lies between that of these two lanthanons.

According to Moeller and Kremers (*Chem. Reviews*, 1945, **37**, 97), Y should theoretically follow Dy in order of decreasing basicity, but examples in which Y occupies a place above Dy are quoted by these authors and by Marsh (*J.*, 1947, 118).

Section B. Column Separations.

Preparation of Lanthanon Mixtures.—The Y, La, Ce, Pr, and Nd material used was as described above. In addition the following samples were available : Technical didymium nitrate (containing 12·5% of CeO_2 and a little La); mixtures of the compositions (*a*) La_2O_3 18, CeO_2 50, Pr_2O_3 8, Nd_2O_3 24%; (*b*) mixed lanthanon sodium sulphates containing Y_2O_3 10, Er_2O_3 17, Tm_2O_3 6·8, Yb_2O_3 57, and Lu_2O_3 10%; (*c*) Y_2O_3 34, Gd_2O_3 40, Dy_2O_3 23, Ho_2O_3 1·9, Er_2O_3 1%.

The lanthanon oxides were converted into nitrates which were dissolved in the eluant before being placed on the column as described in Part V (*loc. cit.*). With (*a*), fuming to dryness with concentrated hydrochloric acid and then with nitric acid was necessary to get the constituents into solution owing to the high Ce content. In (*b*) lanthanon hydroxides were precipitated by alkali, the mixed bases being then centrifuged, washed with water, and dissolved in nitric acid.

Preparation of Cellulose Columns.—The procedure described in Part V was modified. For this work all columns were packed under compressed air or nitrogen with a thin suspension of cellulose in the eluant mixture containing no complex-forming agent. This method was more efficient in eliminating air bubbles from the column, besides being more economical. The complex-containing eluant was run for a few cm. on the column before the mixture of cations was put on.

Analysis of Eluate Fractions.—This was carried out as described in Part V. In separations of lanthanons from Ce, paper-strip analysis was not essential as the first (or last) trace of Ce to be eluted imparted a pale yellow colour to an otherwise colourless lanthanon solution in nitric acid, and a pale green colour to an otherwise bluish-purple didymium solution. The purity of samples was tested by paper-strip chromatography, and selected lanthanon material, which appeared to be pure, was analysed by arc-spectroscopy as a check.

TABLE 3. *Separations of* Y, La, Ce, *and* " Di " (= Pr + Nd) *on narrow columns.*

Column : 100 cm. × 1·5 cm. (int. diam.). Flow rate = 2·5—3·0 ml./hr. on I.C.I. cellulose, 8—9 ml./hr. on " ashless " cellulose.
The cations were eluted in the order : Y, " Di " (Pr or Nd), Ce, La.

Mg. of lanthanon oxide in mixture	Cellulose	Eluant	Mg. of lanthanon oxide recovered in purest fractions	Purity
Pr_6O_{11} 20 La_2O_3 20	I.C.I.	(A)	Pr_6O_{11} 15 La_2O_3 9	Free from La ,, Pr
Nd_2O_3 50 La_2O_3 50	I.C.I.	(A)	Nd_2O_3 30 La_2O_3 30	,, La ,, Nd
Nd_2O_3 50 La_2O_3 50	I.C.I.	(D)	Nd_2O_3 31 La_2O_3 nil	,, La —
" Di_2O_3 " 35 CeO_2 5	I.C.I.	(A)	" Di_2O_3 " 20 CeO_2 nil	,, Ce —
" Di_2O_3 " 35 CeO_2 5	Ashless	(A)	" Di_2O_3 " 22 CeO_2 nil	,, Ce —
" Di_2O_3 " 17·5 CeO_2 2·5 La_2O_3 200	I.C.I.	(A)	" Di_2O_3 " 10 CeO_2 nil La_2O_3 100	,, Ce, La — ,, Ce, Di
Y_2O_3 35 CeO_2 20 La_2O_3 150	I.C.I.	(A)	Y_2O_3 14 CeO_2 nil La_2O_3 not collected	,, Ce, La — —
Y_2O_3 35 CeO_2 20 La_2O_3 150	Ashless	(A)	Y_2O_3 19 CeO_2 nil La_2O_3 not collected	,, Ce, La — —
Y_2O_3 35 La_2O_3 37·5	I.C.I.	(F)	Y_2O_3 25 La_2O_3 12	0·01% La Trace of Y

TABLE 4. *Separations of* Y, La, Ce, " Di " (= Pr + Nd) *on a wider column of ashless cellulose.*

Column : 100 cm. × 5·2 cm. (int. diam.). Flow rate : 100 ml./hr. (20—22 ml. fractions collected).
The cations were eluted in the order : Y, " Di," Ce, La.

Mg. of lanthanon oxide in mixture	Eluant	Mg. of lanthanon oxide recovered in purest fractions	Purity
" Di_2O_3 " 210 CeO_2 30	(A)	" Di_2O_3 " 128 CeO_2 not collected	Free from Ce —
Y_2O_3 420 CeO_2 240 La_2O_3 225	(B)	Y_2O_3 317 CeO_2 not collected La_2O_3 not collected	,, Ce, La — —

Notes on Tables 3 *and* 4.—Technical didymium nitrate constituted the didymium–cerium used; 100 mg. of the nitrate contained 35 mg. of " Di_2O_3 " and 5 mg. of CeO_2.

The yields of didymium diminished if an increase was made in the column load or the cerium content of the mixture (by adding cerous nitrate). Table 5 illustrates this.

Note on Table 5.—From section (*a*) it is noted that ashless cellulose is more efficient than the I.C.I. variety. Owing to the greater flow-rate with the former, the break-through time is considerably reduced.

Resolutions of Mixtures (b) *and* (c).—40 mg. of the oxides of each mixture were converted into nitrates which were run on narrow columns in the usual manner.

Mixture (b). Column (I.C.I. cellulose) 124 cm. Flow rate 2·5 ml./hr. Eluant (C). The cations appeared to be eluted in the order Lu, Yb, (Tm), Y, Er. Early fractions on burning gave white oxides from which colourless nitrate solutions were obtained. Paper-strip

TABLE 5.

(a) Mg. of didymium nitrate run on small column	Yield (%) of " Di_2O_3 " free from Ce obtained		Mg. of didymium nitrate run on small column	Yield (%) of " Di_2O_3 " free from Ce obtained	
Cellulose :	I.C.I.	Ashless	Cellulose :	I.C.I.	Ashless
100	57	63	200	30	43
125	34	46	300	21	not run
150	32	not run	400	14	not run

Mg. of didymium nitrate run on large column	Yield (%) of " Di_2O_3 " free from Ce obtained	Mg. of didymium nitrate run on large column	Yield (%) of " Di_2O_3 " free from Ce obtained
600	61	1500	46
1200	51	3000	33

(*b*) CeO_2 (%) in didymium nitrate (100 mg. run)	Yield (%) of " Di_2O_3 " free from Ce obtained	CeO_2 (%) in didymium nitrate (100 mg. run)	Yield (%) of " Di_2O_3 " free from Ce obtained
12·5 (tech. nitrate alone)	57	37·5	28
25	47	50 [mixture (a)]	15

chromatography yielded with the first 4—5 fractions a deep golden-brown fluorescent zone at $R_F \simeq 0{\cdot}7$ (Lu) and with the rest of the early fractions a dark zone at $R_F \simeq 0{\cdot}7$ (Yb). Later fractions gave pink oxides and nitrate solutions (Er), which on paper-strip analysis yielded a golden fluorescent spot at $R_F \simeq 0{\cdot}5$ (Y).

Mixture (c). Column (ashless cellulose) 100 cm. Flow rate 9 ml./hr. Eluant (B). The cations appeared to be eluted in the order Dy ⟶ Y. Gd, Ho, and Er were not detected with certainty.

Paper-strip analysis on the oxides of the initial fractions mixed with Pr_6O_{11} gave two substantial separate spots which did not fluoresce in ultra-violet light. These were deemed to be Pr (upper) and Dy, as Gd was not separated totally from Pr. Er is usually eluted with Y (see-below), and Ho was thought to be present in too low concentration (<2%) to be solely responsible for the lower spot.

Similar treatment of the oxides from late fractions gave two almost separate spots, an upper one which did not fluoresce in ultra-violet light (Pr) and a lower one which fluoresced golden-yellow (Y).

From the results of the paper-strip and column experiments it is predicted that good separations would be obtained between La or Ce and Pr to Lu (including Y) and between Pr or Sm and Dy to Lu (including Y), provided that the correct conditions of column length, flow rate, and load are observed.

Most of the oxine used could be recovered from the eluates by distillation.

Our grateful thanks are offered to Dr. J. K. Marsh for the gift of lanthanon mixtures of known composition, to Messrs. C. Candler and N. Atherton for the emission spectroscopy of oxides, and to the Ministry of Education for a Maintenance Grant to one of us (H. M. S.).

THE UNIVERSITY, BRISTOL. [*Received, March 11th*, 1954.]

Solubilities of the Inert Gases in Water.

By T. J. Morrison and N. B. Johnstone.

[Reprint Order No. 5273.]

The solubilities of the inert gases in water are accurately represented by an equation of the type proposed by Valentiner. A constant partial molar heat capacity is indicated for all five gases from helium to xenon, though there may be a variation of not more than about 6 cal./deg./mole. Comparison with data obtained by Ostwald's technique suggests that the work of Lannung on helium, neon, and argon is the most reliable, but the temperature ranges he used are too small for reliable estimates of $\bar{c}_p$ to be obtained. The behaviour of the inert gases is compared with that of the paraffin series and other gases. The probable behaviour of carbon tetrafluoride is briefly considered.

During a continuation of the salting-out measurements previously reported (*J.*, 1952, 3814, 3819) it became evident that the solubilities obtained in the inert-gas series showed rather considerable deviations from many results obtained by Ostwald's technique. Since these earlier measurements have been used to calculate the thermodynamic characteristics of these important systems, it is of interest to compare the results from two different techniques.

The results are accurately represented by the type of equation due to Valentiner (*Z. Physik*, 1927, **42**, 253), *viz.*,

$$\log_{10} s_0 = -A + B/T + C \log_{10} T$$

(s_0 = absorption coefficient at 1 atm. per 1000 g. of water), but the constant C is approximately the same for all members, whereas in the paraffin series it is not. With $C = 20{\cdot}5$, and the constants A and B shown in Table 1, deviations between experimental and calculated values are generally within $\pm 0{\cdot}5\%$ in s_0 and show little or no trend. In view of the possible error in estimating C, there may be slight differences between the gases, but it is doubtful if these can exceed 3 units from helium to xenon. Fig. 1 shows differences between experimental and calculated values of $\log s_0$ ($\Delta \log s_0$) and also deviations of certain recorded values.

Table 1.

Gas	He	Ne	A	Kr	Xe
A	58·987	59·412	60·272	60·434	60·836
B	2740	2890	3290	3410	3605

The following comparisons with previously recorded data may be made.

Helium.—The results of von Antropoff (*Z. Electrochem.*, 1905, **14**, 585; 1919, **25**, 269; *Proc. Roy. Soc.*, 1910, **83***A*, 474) and of Estreicher (*Z. physikal. Chem.*, 1899, **31**, 176), which are commonly quoted, show deviations of about +10% and +50%, respectively, and are not included. The results of Lannung (*J. Amer. Chem. Soc.*, 1930, **52**, 68) and of Cady, Elsey, and Berger (*ibid.*, 1922, **44**, 1456) are, however, in reasonable agreement, and suggest from their scatter that the present values in the range 10—30° c are accurate. Individual runs by these workers vary by about $\pm 1\%$ from their mean values. The only recorded measurements of value in the range 30—75° are those at high pressures by Wiebe and Gaddy (*ibid.*, 1935, **57**, 847; 25—1000 atm.) and by Pray, Schweickert, and Minnich (*Ind. Eng. Chem.*, 1952, **44**, 1146; 100—500 lb./sq. in.). Extrapolation to 1 atm. gives rise to slight uncertainty, but suggests that our values in this range are not greatly in error.

Neon.—Our results are in agreement with those of Lannung in the range 10—45°. Data by von Antropoff and by Valentiner, showing very high temperature coefficients in opposite directions, cannot be conveniently included in full in Fig. 1, and there are no other measurements of value above 45°.

Argon.—There is again good agreement with Lannung's results in the range 10—45°. An identical value by Eucken and Herzberg (*Z. physikal. Chem.*, 1950, **195**, 1) at 20° confirms the accuracy. The results of Winkler (*ibid.*, 1906, **55**, 347), Estreicher and Akerlof (*J. Amer.*

FIG. 1.

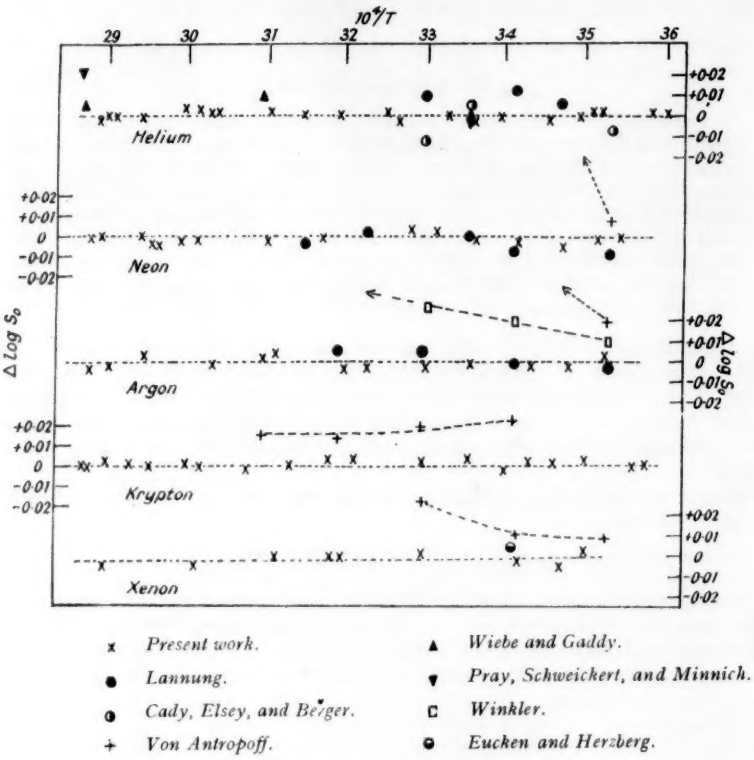
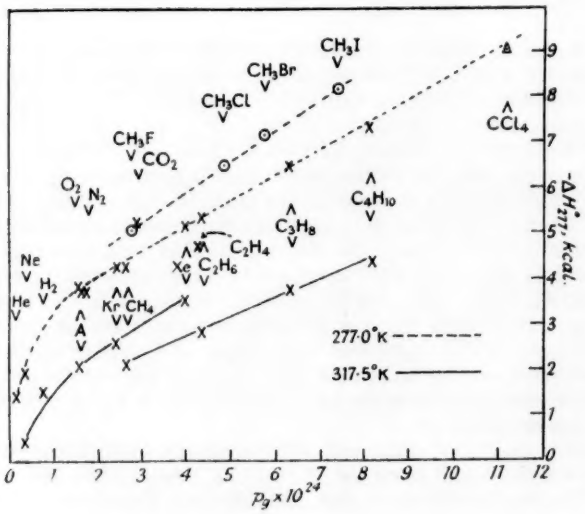

10⁴/T
29
30
31
32
33
34
35
36
Helium
Neon
Argon
Krypton
Xenon
Δ Log S₀
Δ Log S₁₀
+0·02
+0·01
0
-0·01
-0·02
Present work.
Lannung.
Cady, Elsey, and Berger.
Von Antropoff.
Wiebe and Gaddy.
Pray, Schweickert, and Minnich.
Winkler.
Eucken and Herzberg.

FIG. 2.

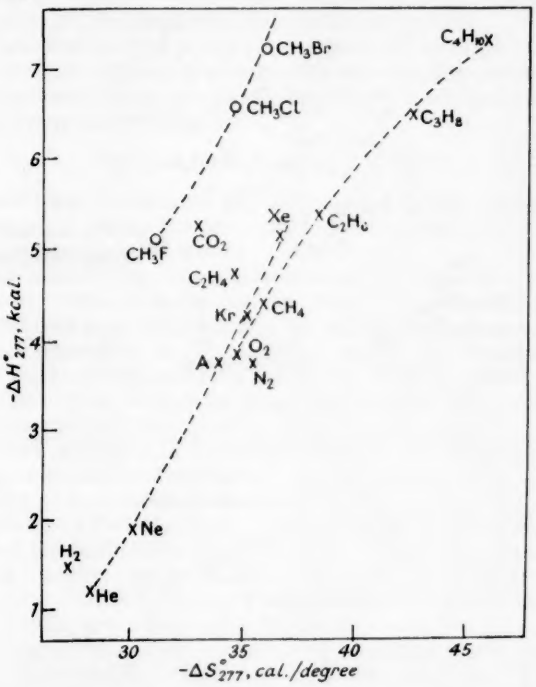

CH₃I
CH₃Br
CH₃Cl
CCl₄
CH₃F
CO₂
O₂
N₂
C₄H₁₀
C₃H₈
C₂H₄
C₂H₆
Xe
Ne
H₂
He
Kr
CH₄
A
277·0°K
317·5°K
-ΔH₂₇₃°, kcal.
p₂ × 10²⁴
0
1
2
3
4
5
6
7
8
9
10
11
12

Chem. Soc., 1932, **54**, 4129), and von Antropoff are considerably higher. It is noteworthy also that values in the region of 0—2° by Lannung, Eucken, and Herzberg, and by Sisskind and Kasarnowsky (*Z. anorg. Chem.*, 1931, **200**, 282) are in excellent agreement with our equation.

Krypton and Xenon.—Our results are considerably lower than those of von Antropoff. Eucken and Herzberg, however, record a value for xenon at 20° which is within 1% of our figure.

It therefore appears that the work of Lannung on helium, neon, and argon is the most reliable general investigation in this series by the Ostwald technique, and the solubilities of these gases may be regarded as having been accurately established by two different tech-

FIG. 3.



niques in the temperature range 10—45°. Little reliance can be placed on the data of von Antropoff which agree neither with those of Lannung nor of ourselves.

It is clearly of considerable importance to decide whether the partial molar heat capacity varies in this series by some 40—60 cal./deg. from helium to xenon as calculated by Eley (*Trans. Faraday Soc.*, 1944, **40**, 184) and by Glew and Moelwyn-Hughes (*Discuss. Faraday Soc.*, 1953, **15**, 150), or is approximately constant. It appears that these calculations were based on the experimental results of Estreicher, von Antropoff and Valentiner, and these have been shown to bear little resemblance to more modern values obtained by two different techniques. In the case of helium it can be shown that if the results in the range 10—30° are accepted, a value of $\bar{c}_p$ of 24 cal./deg. (Glew and Moelwyn-Hughes) would lead to discrepancies of the order of 3% at 50° and 8% at 70°. For xenon, $\bar{c}_p = 65$ cal./deg. being used, the corresponding discrepancies would be 7% and 16%. These would, of course, be in opposite directions, and it appears unlikely that some unsuspected source of error at higher temperatures would operate in this way. It seems to us that the variation between

helium and xenon does not exceed 6 cal./deg. and is probably less. In the paraffin series there appears to be a real variation of some 20 cal./deg. from methane to *n*-butane.

Although comparisons of thermodynamic characteristics are often made at 25°, the theory put forward by Eley (*Trans. Faraday Soc.*, 1939, **35**, 1421; 1944, **40**, 184) on the mechanism of gas solubilities, suggests that it might be profitable to compare heats and entropies of solution at 4°, the temperature at which, according to Eley, there is little or no

FIG. 4.

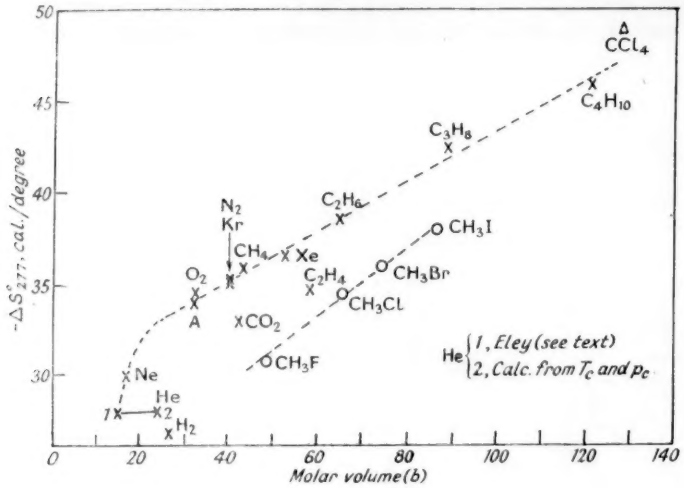
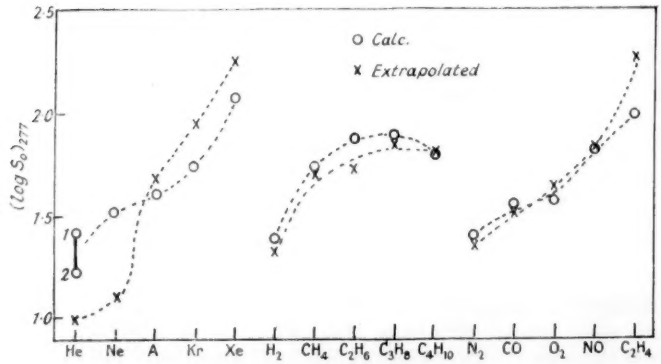


FIG. 5.



energy or entropy change in forming cavities in the solvent. We have therefore calculated values of ΔH°_{277} and ΔS°_{277} (mole-fraction, 1 atm. pressure) using the constants of Table 1, and the corresponding values for the paraffins and other gases (*J.*, 1952, **3814**). While a slight extrapolation (not more than about 8°) is necessary, we may relate ΔH°_{277} with Eley's ΔE_A (energy of interaction between gas and water molecules), and ΔS°_{277} with Eley's ΔS_A of interaction, without assumptions about partial molar volumes and the exact mechanism of cavity formation. Fig. 2 shows that ΔH°_{277} is a smooth function of polarisability for all the non-polar gases and becomes almost linear with P_g above argon. A point for carbon tetrachloride (Gross and Saylor, *J. Amer. Chem. Soc.*, 1931, **53**, 1744) also lies on this line. The polar halides, CH_3X (Glew and Moelwyn-Hughes, *Discuss. Faraday Soc.*, 1953,

15, 150), and carbon dioxide have appreciably higher values of ΔH°_{277}. Eley (*ibid.*, p. 263) has obtained a similar relation by subtracting calculated values of the energy of cavity formation (ΔE_C) from observed values of ΔE°_{298}. Because of the different partial molar heat capacities of the inert gases and the paraffins, the smoothness of the relation shown in Fig. 2 is soon destroyed when the temperature is altered. At 317·5° K, for example ($1/T = 31{\cdot}5 \times 10^{-4}$), Fig. 2 shows that the two series of gases occupy quite distinct lines. It appears to be an interesting confirmation of Eley's views that the smoothest relation with polarisability is obtained for all the non-polar gases in the region of 277° K.

The parallelism between ΔH°_{277} and ΔS°_{277} suggested by the work of Barclay and Butler (*Trans. Faraday Soc.*, 1938, **34**, 1445) and Frank and Evans (*J. Chem. Phys.*, 1945, **13**, 478) is very approximate, and the two series of gases appear to lie on separate curves (Fig. 3). There appears, however, to be a relation between ΔS°_{277} and molecular volume. In the absence of partial molar volumes, we have used the van der Waals constant b as a measure of volume (Fig. 4) and obtain a linear relation from argon upwards.

The relations indicated in Figs. 2 and 4 are sufficiently accurate to reproduce at least qualitatively the essential differences in solubility between the various non-polar gases. Taking the linear portions of these graphs, we find that the solubility at 277° K should be represented by the approximate equation :

$$\log s_0 = 1{\cdot}845 + 0{\cdot}455p_g - 0{\cdot}0309b$$

and in Fig. 5 we have plotted calculated and extrapolated values of $\log s_0$ against arbitrary scales for three groups of gases—the inert gases, the paraffins, and a group of gases of approximately the same molecular weight.

The tendency for solubility to rise with the mass of the molecule in the inert-gas series, while it remains nearly constant in the paraffin series at this temperature, is shown. In the group of miscellaneous gases the relatively low solubility of nitrogen and the high solubility of ethylene are reproduced in the calculated figures. It is somewhat surprising to find that, although the heat and entropy of solution of hydrogen would not be given even to a first approximation by the linear relations of Figs. 2 and 4, yet the calculated solubility is in reasonable agreement with that found. Ethylene behaves rather similarly.

The rather unusual properties of carbon tetrafluoride and similar gases would afford another test of the empirical relations given. Carbon tetrafluoride, for example, has a relatively low electron polarisability, probably about the same as that of methane, while its volume approximates to that of ethane. Using the corresponding heat and entropy of solution, we find that the predicted solubility is of the order of 10 c.c. per 1000 g. of water at 277° K. This will fall fairly rapidly because of the heat of solution of about 4 kcal. and at 25° C should be about 6 c.c. Preliminary experiments have shown that this gas is certainly less soluble than helium with a solubility at 25° C of about 4·5 c.c. The very low solubility at high temperature raises experimental problems which must be overcome before the complete thermodynamic behaviour can be reported, but it appears from the results already available that the solubility is slight less than the predicted value, probably owing to a heat of solution which is somewhat less than would be obtained from the polarisability. A similar treatment applied to sulphur hexafluoride suggests that this gas would have a solubility of the same order.

Experimental

The modified apparatus described by Morrison and Billett (*J.*, 1952, 3819) was used. The inert gases were obtained from the British Oxygen Co. Ltd. and were " spectroscopically pure " in the cases of helium, neon, and argon. The krypton was 99—100% pure, the residue being xenon, while the xenon contained about 1% of krypton. In the case of krypton, the impurity is more soluble and will gradually be removed from the system. For 0·5% of xenon impurity the discrepancy in solubility would not be detected and no correction is therefore applied. The impurity in the xenon may, however, lead to an appreciable error since the krypton will tend to accumulate in the gas. A correction of +0·002 in $\log s_0$, corresponding to 1% of krypton, has been applied to the observed solubilities, and calculations based on the amount of water brought into contact with the gas suggest that the accumulation of krypton was not sufficient to justify

further correction. Determinations with helium and with krypton were carried out with two separate samples of each gas (*a* and *b* in Table 2). Temperatures were not systematically raised or lowered for successive runs, but were " scattered " so that any impurity accumulating in the gases might be detected.

TABLE 2. *Solubilities of gases (in c.c. at N.T.P.) per* 1000 *g. of water at a gas pressure of* 1 *atm.* (s_0).

$t°$, C	s_0	$t°$, C	s_0	$t°$, C	s_0	$t°$, C	s_0	$t°$, C	s_0
Helium		*Neon*		*Argon*		*Krypton*		*Xenon* (corr. to 100% Xe)	
4·6	9·44 *b*	9·1	11·7	10·7	40·9	6·6	82·0 *a*	12·7	135·5
6·0	9·35 *b*	11·5	11·3	14·3	37·2	8·0	79·4 *b*	15·1	123·6
11·0	9·04 *b*	15·0	10·9	18·2	34·6	12·6	69·5 *a*	15·5	121·1
12·0	8·97 *a*, *b*	19·8	10·6	24·4	31·1	15·5	65·6 *a*	19·6	110·9
13·2	8·87 *a*	24·4	10·2	29·8	28·3	18·2	61·7 *b*	30·2	84·5
16·6	8·71 *a*, *b*	28·8	10·1	36·6	25·9	21·2	58·2 *a*	40·0	69·3
21·7	8·53 *a*	31·3	9·93	39·4	25·1	24·7	53·5 *a*	40·5	67·8
24·7	8·47 *a*, *b*	32·1	9·93	47·8	23·1	30·2	48·9 *a*	47·9	59·4
27·4	8·45 *a*	42·1	9·48	49·5	22·6	35·4	44·3 *a*	59·0	50·8
33·0	8·34 *a*	49·5	9·40	56·3	21·3	41·4	40·6 *a*	71·7	43·8
34·6	8·41 *b*	58·8	9·46	66·3	20·2	46·0	38·3 *b*		
40·4	8·41 *a*	61·0	9·44	71·3	19·4	51·9	35·9 *a*		
44·9	8·45 *b*	64·4	9·55	74·1	19·1	57·9	33·3 *a*		
48·9	8·59 *a*	65·4	9·53			59·8	32·8 *a*	*Carbon tetrafluoride*	
54·4	8·71 *b*	66·6	9·57			64·7	31·6 *a*	6·7	6·5
55·9	8·81 *a*, *b*	72·5	9·84			67·5	30·7 *b*	13·1	5·6
58·6	8·89 *b*	74·1	9·84			71·5	29·7 *a*	19·0	5·0
60·5	9·02 *a*					73·9	29·5 *a*	24·7	4·5
67·4	9·23 *a*					74·9	29·3 *b*	38·5	3·7
70·5	9·42 *b*								
71·4	9·42 *a*								
73·0	9·46 *b*								

The carbon tetrafluoride used was supplied by Imperial Chemical Industries Limited in the form of " Arcton O." Because of the extremely low solubility, some modification of the apparatus may be required, and the results given are provisional, with possible errors of ±2%.

DUNDEE TECHNICAL COLLEGE. [*Received, April 2nd,* 1954.]

The Chromatography of Gases and Vapours. Part IV. Applications of the Surface-potential Detector.*

By J. H. GRIFFITHS and C. S. G. PHILLIPS.

[Reprint Order No. 5296.]

The paper describes a device for the detection and estimation of vapours in nitrogen. Its action depends upon changes in the surface-potential difference between two metal plates, one of which is vibrating close to the other. Its application to gas chromatography is discussed and illustrated. It has also been used to determine vapour pressures.

IN previous work in this series (Phillips, *Discuss. Faraday Soc.*, 1949, **7**, 241; James and Phillips, *J.*, 1953, 1600; *J.*, 1954, 1066) the separations, achieved by the gas chromatographic columns, have been followed by means of a thermal-conductivity cell placed at the exit of the column. Although the thermal-conductivity cell is sensitive to small concentrations of vapour and readily lends itself to continuous recording, we have found that the limits of our gas-chromatographic work have largely been set by the limits of the thermal-conductivity recording system. We therefore decided to investigate a number of other methods for detecting small concentrations of vapour in nitrogen. Some of our initial results with various detectors have already been reviewed (Griffiths, James, and Phillips, *Analyst.*, 1952, **77**, 897). This paper is concerned with the surface-potential

* Part III, *J.*, 1954, 1066.

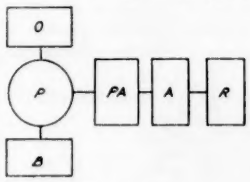
vapour detector, and in particular with its application to gas chromatography. The possibility of using changes in surface potential for detecting small vapour concentrations was first suggested to us by the work of G. Phillips (*J. Sci. Instr.*, 1951, **28**, 342), and we have followed his design in constructing much of our detector system.

Principle of Operation of the Surface-potential Detector.—If two identical metal plates are connected by a conductor, and one plate is made to vibrate close to the other, no current flows in the conductor. The potential at the surface of each plate will be the same, so that the vibrating plate is moving in zero field. If, however, the two plates are dissimilar (*e.g.*, two different metals, or a surfaced and an unsurfaced plate), the two surfaces will no longer have the same potential and an alternating E.M.F. will be set up in the conductor on vibration. The standing difference in surface potential can be measured by applying a bias E.M.F. to one of the plates until the alternating E.M.F. is reduced to zero. If the surfaces are now changed by exposure to an adsorbable vapour, the standing potential will, in most cases, also be changed. This change in potential is the signal of the surface-potential detector.

Experimental

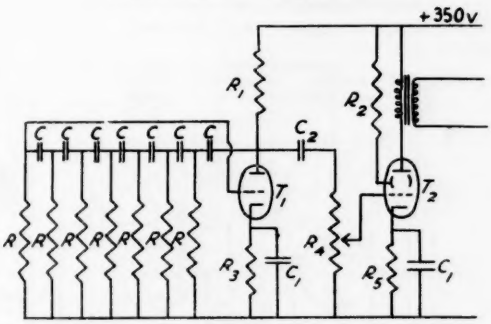
Apparatus.—Fig. 1 is a block diagram of the complete detector. The vibrating plate is attached to a microphone which is driven (200—500 cycles) by a straightforward phase-shift

Fig. 1. *Block diagram of apparatus.*



O, Oscillator.
P, Plate assembly.
B, Bias control.
PA, Preamplifier.
A, Amplifier.
R, Recorder.

Fig. 2. *Phase-shift oscillator.*



T_1, 6J5. T_2, 6V6.
C, 1,500 p F. C_1, 50 μF. C_2, 0·1 μF.
R, 470 K. R_1, 200 K. R_2, 1K.
R_3, 4·7 K. R_4, 1 M. R_5, 220 Ω.

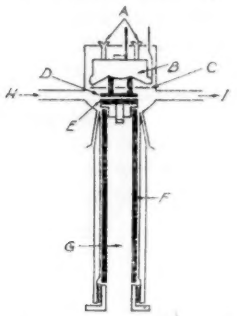
oscillator (Fig. 2). The plate assembly is illustrated in Fig. 3. The electrode system is made as compact as possible in order to reduce the dead volume which has to be swept out with gas. A dead volume of *ca.* 20 ml. is achieved by driving the 1″-diameter vibrating electrode with a small moving-coil headphone, the cone of which forms the "roof" of the glass electrode chamber; the stationary electrode protrudes through the bottom of the chamber to within 0·01 cm. of the vibrating plate, and is supported by an ebonite tube within a steel cylinder. The steel cylinder is ground to a standard taper and fits tightly into the ground socket which forms the bottom of the electrode chamber. The ebonite tube which supports the stationary electrode contains the first stage of amplification (Fig. 4, an E.T.3. electrometer triode, battery-driven for stability) and can be moved up and down within the steel cylinder to adjust the gap between the electrodes. The electrode region is completely screened by sheets of earthed copper foil and by silver deposited on the inside of the glass chamber.

The output from the plates is applied to the grid of the electrometer triode (preamplifier), and the output of the preamplifier is fed to an R–C coupled three-stage amplifier (Fig. 5), the first stage of which is an EF 37A low-noise pentode. The output of the amplifier is rectified, and fed to a D.C. milliammeter pen-recorder. Bias E.M.F. is applied to the plates by means of a calibrated potentiometer.

Plate Surfacing.—Although we have carried out experiments with a number of different

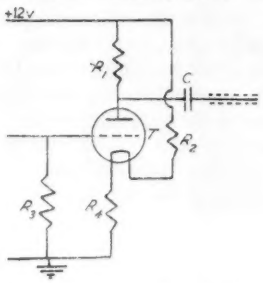
plate surfaces, we have, in most of our work, used a detector containing two steel plates, one of which is surfaced with stearic acid or with octadecanol. The stearic acid or octadecanol is applied by the rubbing method recommended by Menter and Tabor (*Proc. Roy. Soc.*, 1951, **204**, *A*, 514). Both sets of plates prove to be highly reproducible, and are very easily prepared.

FIG. 3. *Plate assembly.*



A, Levelling screws. *B*, Headphone.
C, Copper screening. *D*, Vibrating plate.
E, Stationary plate. *F*, Ebonite cylinder.
G, Electrometer and pre-amplifier assembly. *H*, Gas inlet.
I, Gas outlet.

FIG. 4. *Preamplifier.*



T, ET3. *C*, 0·1 μF.
R_1, 47 K. R_2, 300 Ω.
R_3, 10^{10}Ω. R_4, 80 Ω.

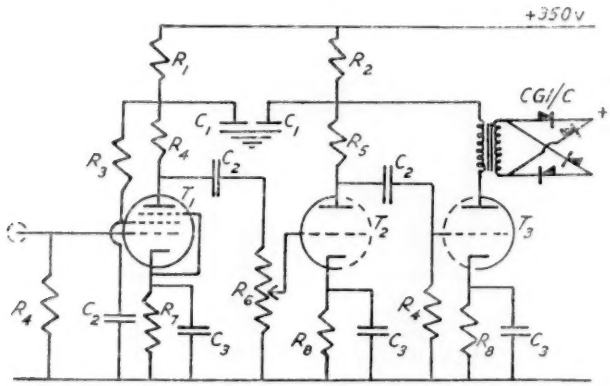


FIG. 5. *Amplifier.*

T_1, EF 37A.
T_2, T_3, two halves of 6SN7.
C_1, 8 μF.
C_2, 0·1 μF.
C_3, 50 μF.
R_1, 47 K.
R_2, 22 K.
R_3, 2·2 M.
R_4, 470 K.
R_5, 100 K.
R_6, 330 K.
R_7, 4·7 K.
R_8, 3·3 K.

RESULTS AND DISCUSSION

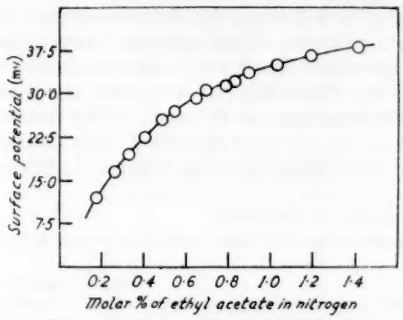
Some typical results are given in Table 1. These have been obtained by passing, between the plates, nitrogen which has been saturated at 0° with the vapours of the various substances. (These have largely been selected because of their suitability for later chromatographic work). The signals obtained are, for the most part, very well above the drift noise-level of the present instrument (1 mv). The figures quoted are for the potentials which must be applied to the unsurfaced steel plate to restore the output to zero.

The results for any one set of plates tend to fall into three groups: positive signals (esters and ethers), zero signals (non-polar substances), and negative signals (chlorinated compounds). Within the series of esters, it is to be noted that there is no marked falling off of signal with increase of molecular weight (and hence decreasing vapour pressure at 0°). This must mean that the reduced vapour pressure is to some extent counterbalanced by increased adsorption on the plates. Thus ethyl oxalate, whose vapour pressure is 4×10^{-2} mm., produces a signal of the same order of magnitude as ethyl acetate, which has a vapour pressure of 24 mm. Although both sets of plates give somewhat similar results,

the stearic acid/steel set being slightly more sensitive, there are a number of differences between the two sets, the most marked of which is the reversal of sign observed with aniline.

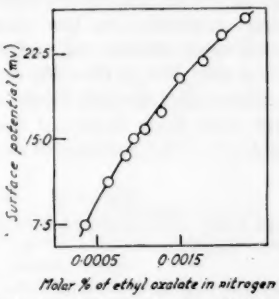
Relation between Surface Pontential and Concentration.—The relation between the surface-potential change and the concentration of vapour has been determined for a number of substances. Figs. 6, 7, and 8 illustrate the relations, or surface-potential isotherms, obtained for ethyl acetate, ethyl oxalate, and chloroform on the stearic acid/steel set of plates. All the isotherms prove to be of the same type, suggesting an

FIG. 6. *Surface-potential isotherm for ethyl acetate.*



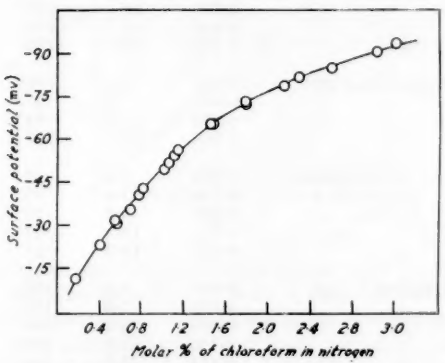
Detector plates: stearic acid/steel.

FIG. 7. *Surface-potential isotherm for ethyl oxalate.*



Detector plates: stearic acid/steel.

FIG. 8. *Surface-potential isotherm for chloroform.*



Detector plates: stearic acid/steel.

FIG. 9. *"Langmuir" plot for ethyl acetate.*

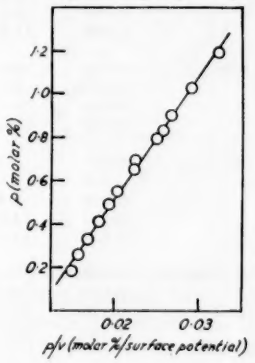


TABLE 1. *Response of detector to various vapours.*

(Values quoted are for saturated vapour pressures at 0°, and represent the potentials which must be applied to the unsurfaced plate to return the output signal to zero.)

Vapour	Surface potential (mv) * (A)	(B)	Vapour	Surface potential (mv) * (A)	(B)
Ethyl acetate	70	43	Decalin	0	0
*cyclo*Hexyl acetate	96	160	Benzene	0	0
"Cellosolve" acetate	30	80	Carbon tetrachloride	0	0
*iso*Amyl *n*-butyrate	62	110	Chloroform	−84	−140
n-Amyl *n*-butyrate	52	96	*m*-Dichlorbenzene	−12	− 60
Methyl benzoate	26	20	*o*-Dichlorbenzene	− 6	− 30
Ethyl oxalate	40	34	2:2′-Dichlorodiethyl ether	−10	− 34
Ethyl malonate	66	68	3:3′-Dichlorodipropyl ether	−18	− 76
Amyl ether	8	0	Aniline	20	− 50
Phenetole	8	20			

* (A) = Octadecanol/steel surface; (B) = stearic acid/steel surface.

approach to a limiting value for the surface-potential change at high vapour concentrations. The isotherms resemble single adsorption isotherms, though we are concerned with two surfaces. Moreover, if p is plotted against p/v as is customary for Langmuir-type adsorption, reasonable straight lines are obtained as is shown for example in Fig. 9 for the case of ethyl acetate. (The corresponding B.E.T. plots are more curved). From such plots we have estimated values for the saturation surface potentials (for plates at room temperature, 17°). These values are (in mv): chloroform 187, water 60, ethyl acetate 55, ethyl oxalate 47, ethyl methyl ketone 38, *iso*amyl acetate 47.

Application to Chromatography.—Because of the sensitivity of the detector to low vapour concentrations, the scale of gas chromatography may be considerably reduced. We have, therefore, largely concentrated on its use for following the chromatography of high-boiling substances on low (room)-temperature columns. Such columns have to be packed with weak adsorbents, and we have used either sand (graded by sedimentation in a stream of water, B.S.S. 60—80) or small glass beads (Ballotini, No. 15 grade, less than 0·1 mm. diam., The English Glass Co., Ltd., Leicester) in most of the work. The various substances have been displaced from these columns by nitrogen saturated with diethyl malonate at 0°. The columns of sand have proved quite satisfactory for esters, as is shown

TABLE 2. *Displacement analyses on Ballotini.*

[Column temp. 15°; displacer, diethyl malonate (saturation at 0°); flow rate of nitrogen, 68 ml. min.; detector plates, stearic acid/steel.]

Substance and step height (mv)	Quantity, μl.	Step length, min.	Specific length, min./μl.	Substance and step height (mv)	Quantity, μl.	Step length, min.	Specific length, min./μl.
Methyl benzoate	0·060	2·4	40	" Cellosolve "	0·072	7·2	100
(+ 20)	0·072	3·0	42	acetate (+ 26)	0·096	9·8	102
	0·114	5·6	49		0·120	12·8	107
	0·168	8·0	48		0·138	14·1	102
	0·240	11·0	46		0·186	19·2	103
					0·192	19·6	102
n-Amyl butyrate	0·072	6·0	83				
(+ 30)	0·108	9·0	84	Amyl ether (0)	0·036	3·4	95
	0·144	11·6	81		0·072	7·0	97
	0·180	14·4	80		0·120	11·2	94
					0·168	18·0	107
*iso*Amyl butyrate	0·060	5·2	87				
(+ 36)	0·084	7·0	83	3 : 3′-Dichlorodi-	0·108	5·2	48
	0·096	8·4	87	propyl ether	0·156	7·0	45
	0·144	11·8	82	(− 30)	0·234	9·2	39
	0·150	11·6	78		0·270	11·0	41
					0·354	13·2	37
*cyclo*Hexyl acetate	0·048	4·6	96				
(+ 24)	0·084	8·2	98	Aniline (− 28)	0·060	6·4	107
	0·120	11·0	92		0·072	7·8	108
	0·144	14·0	97		0·090	9·8	109
					0·120	12·8	107
					0·144	16·2	112
					0·168	17·0	101
				*cyclo*Hexanone	0·048	12·8	270
				(+ 10)	0·084	20·0	240
					0·108	26·0	240
					0·132	31·0	235

by the results plotted in Fig. 10, but 3 : 3′-dichlorodipropyl ether, *cyclo*hexanone (Fig. 11), methyl*cyclo*hexanone, and aniline appear to be somewhat irreversibly adsorbed. This irreversible adsorption would appear to be confirmed by the following observations:

(i) The displacer moves more rapidly through a column containing one of these substances; for instance, for a 0·5-g. column of sand, the displacer normally (clean column or only reversibly adsorbed substances on the column) takes 46 min. to break through. If aniline is present this value is reduced to 37 min., or if *cyclo*hexanone is present to 42 min.

(ii) Only poor separations are achieved with mixtures involving one of these substances, when chromatographed on sand.

(iii) On a 0·5-g. column the calculated amounts of methyl*cyclo*hexanone and of 3 : 3′-

dichlorodipropyl ether irreversibly adsorbed are 100 and 92 μg. respectively. On a 1·0-g. column these values become 200 and 188 μg.

On Ballotini all the substances so far investigated seem to be reversibly adsorbed, *i.e.*, the plot of step length against quantity passes through the origin. Some typical results are collected in Table 2. On Ballotini, the following displacement sequence is observed (the figures given in parentheses are the b. p.s.): butyl acetate (126°), amyl acetate (142°), amyl ether (188°), 2 : 2′-dichlorodiethyl ether (178°) *cyclo*hexanone (156°), methyl*cyclo*hexanone (169°), *cyclo*hexyl acetate (175°), *iso*amyl butyrate (185°), *n*-amyl butyrate (185°), methyl benzoate (199°), 3 : 3′-dichlorodipropyl ether (187°), ethyl oxalate (185°), and aniline (184°), followed by diethyl malonate (199°) displacer. From mixtures, the vapours leave the column in this order, only ethyl oxalate and aniline not being clearly separated from one another.

Determination of Latent Heats and Vapour Pressures.—The surface-potential detector has also proved useful for the determination of latent heats and vapour pressures.

(a) *Latent heats.* To determine a latent heat, the signal corresponding to a nitrogen

FIG. 10. *Plot of step-length against quantity in displacement analysis of* isoamyl n-*butyrate* (○) *and methyl benzoate* (●) *from columns of sand.*

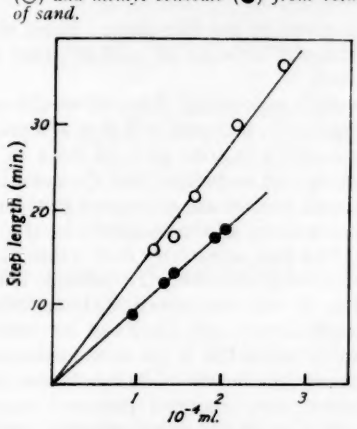
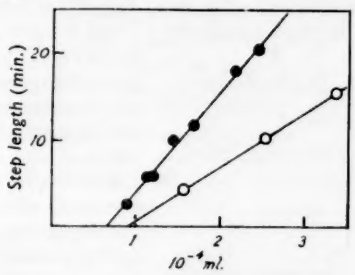


FIG. 11. *Plot of step-length against quantity in displacement analysis of* cyclo*hexanone* (●) *and* 3 : 3′-*dichlorodipropyl ether* (○) *from columns of sand.*



stream saturated with the vapour at $T°$ is first obtained. A stream of nitrogen saturated with the vapour at $(T + t)°$ is then diluted with a second nitrogen stream, until it produces the same signal. From the dilution required and the difference in temperature $t°$, the latent heat is readily computed; *e.g.*, for ethyl oxalate the ratio (Saturated vapour pressure at 30°)/(Saturated vapour pressure at 20°) obtained from the dilution experiments is 2·30 ± 0·02, which gives a value for the latent heat of 14·70 ± 0·15 kcal. (Stoll, *Ind. Eng. Chem.*, 1947, **39**, 517, gives a mean value of 14·65 kcal. at 45—70°). The chief merit of the detector in this connection would seem to be the ease with which latent heats can be determined at temperatures well below the b. p. Values of such latent heats are of interest because of the light they throw on problems of liquid structure (cf. Staveley and Tupman, *J.*, 1950, 3597).

(b) *Vapour pressures.* The determination of latent heats depends upon obtaining an accurate value for the *ratio* of the vapour pressures at $T°$ and $(T + t)°$. To obtain absolute values of the vapour pressures the chromatographic column can be employed. A steady stream of nitrogen, saturated with the vapour at the required temperature, is passed on to the column for a measured number of minutes. The vapour is thus adsorbed, and is then displaced from the column, and its step length in the displacement chromatogram determined. This step length is then compared with the step length produced by a known weight of the same substance. Thus for ethyl oxalate (average values from a number of experiments) the following results were obtained: Nitrogen saturated with

ethyl oxalate at 0°, and flowing at a rate of 65 ml./min. (at 0°) was passed on to the column. The step length obtained was 1·78 min./min. of original saturated flow; $1{\cdot}3 \times 10^{-4}$ g. of ethyl oxalate (*M*, 146) produces a step length of 10·50 min. Hence the vapour pressure at 0° (the gas laws being assumed to hold for such a dilute vapour) is given by the relation

$$\frac{760 \times 1{\cdot}78 \times 1{\cdot}3 \times 10^{-4} \times 22{\cdot}4 \times 10^{3}}{10{\cdot}50 \times 146 \times 65} = 3{\cdot}9 \times 10^{-2} \text{ mm.}$$

Some typical values obtained in this way are given in Table 3. So far as we have been able to discover, these vapour pressures have not been measured before, but we also give

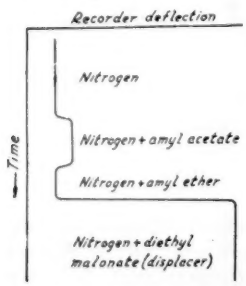
TABLE 3. *Vapour pressures determined by displacement chromatography.*

Substance	Satd. v. p. at 0° (mm.)	Extr'd. values	Substance	Satd. v. p. at 0° (mm.)	Extr'd. values
Ethyl oxalate	0·039	0·020	2 : 2′-Dichlorodiethyl ether	0·12	0·17
Methyl benzoate	0·049	0·047	3 : 3′-Dichlorodipropyl ether	0·091	—
n-Amyl butyrate	0·11	—	Aniline	0·079	0·053
*iso*Amyl butyrate	0·11	0·20	" Cellosolve " acetate ...	0·331	—
*cyclo*Hexyl acetate	0·29	—	*iso*Amyl ether	0·195	0·26
*cyclo*Hexanone	0·73	0·91			

in the Table some values extrapolated from values given in the literature. Since these extrapolations have been made over a temperature range of between 25° and 40°, they are, of course, only very rough approximations.

Conclusion.—The most important feature of the surface-potential detector would seem to be its *high sensitivity*. Thus 4 p.p.m. of ethyl oxalate in nitrogen will give a signal of 7·5 mv. This represents a signal to noise ratio of 7·5/1 in our present experimental detector, but we believe that the noise level can be considerably improved, and we are at present working on an improved detector which we hope will have a noise level of the order of one microvolt. The high sensitivity is of value in gas chromatography for the following reasons: (1) Columns can be operated with the vapours at very low concentrations, with a corresponding increase in efficiency. (2) They can be operated at temperatures considerably below the b. p.s of the substances to be separated. This means that thermolabile substances (such as must be distilled under very reduced pressure) can be conveniently handled. (3) The gas chromatographic method need require only very small samples for an analysis.

FIG. 12. *Displacement analysis of substance with zero signal.*



As has been shown above, the detector is also often highly *selective*, so that its use has a certain diagnostic value (for example, distinguishing chloro-compounds from esters). This selectivity can be most important in displacement analysis, where successive steps frequently have similar concentrations. In particular, it makes it an easy matter to employ a " marker " technique, in which, say, a chloro-compound is chosen so as to place a trough between similar steps produced by two esters otherwise adjacent in the displacement sequence. It is to be noted that substances which give zero signal on the detector can still be handled by the method if in suitable admixture with " active " components, as shown in Fig. 12.

In comparison with thermal conductivity, its main disadvantages are sluggishness, non-linearity of response, and, in a few instances, irreversibility.

Sluggishness. A certain time always elapses before the detector comes into equilibrium with the gas stream passing between the plates. This is to some extent due to the fact that it takes some time to fill the plate assembly. The lag is particularly marked in the desorption of high-boiling substances from the plates. Thus the removal of the acetone signal has a time constant (time to fall to 1/e of maximum) of 30 sec., while for ethyl oxalate the value is 4·5 min. (In both cases flow-rate of 68 ml./min.).

Irreversibility. Aldehydes have been found to produce an irreversible signal, so that

the plates have to be resurfaced after use. This is presumably due to irreversible adsorption, such as we have already experienced on chromatographic columns (Phillips, *Discuss. Faraday Soc.*, 1949, **7**, 241).

Non-linearity. As will be seen from Figs. 6, 7, and 8, the response curve is not linear (as it is with thermal conductivity). This factor, combined with the sluggishness, militates against its use for accurate partition work, where rapid concentration changes (peaks) have to be followed. Most of our work has therefore been done by using adsorbent columns and the displacement technique.

Throughout all our work we have had very great assistance from Mr. G. Phillips (S.R.D.E., Christchurch, Hants). One of us (J. H. G.) is indebted to the Department of Scientific and Industrial Research for a maintenance grant. We thank Imperial Chemical Industries Limited for the loan of a recorder.

INORGANIC CHEMISTRY LABORATORY, OXFORD. [*Received, April 12th*, 1954.]

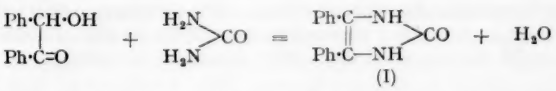
Studies in Stereochemical Structure. Part XI. Heterocyclic Compounds from Benzoin.*

By ROBERT ROGER, KENNETH C. REID, and ROBERT WOOD.

[Reprint Order No. 4303.]

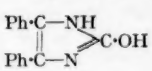
(−)-Benzoin and urea in boiling glacial acetic acid yield optically inactive 2 : 3-dihydro-2-oxo-4 : 5-diphenylglyoxaline. We have found, however, that (−)-benzoin is racemised in glacial acetic acid. The dienolic formula for benzoin explains the accepted structure for the glyoxaline and its racemisation. Most important is the fact that substituted benzoins, *e.g.*, ethylbenzoin, do not condense with urea, probably because they cannot react in an enolic form.

THE formation of 2 : 3-dihydro-2-oxo-4 : 5-diphenylglyoxaline from *rac.*-benzoin and urea is usually depicted as :

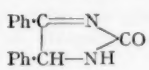


(I)

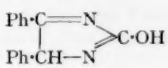
(Biltz, *Annalen*, 1909, **368**, 173; Chattaway and Coulson, *J.*, 1929, 1363). Three other formulations for the glyoxaline (II—IV), however, are possible, (III) and (IV) possessing centres of asymmetry and (II) and (IV) conjugated double-bond systems.



(II)

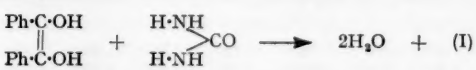


(III)



(IV)

The condensation of (—)-benzoin with urea was carried out just as with *rac.*-benzoin *viz.*, by boiling in glacial acetic acid for some hours, the glyoxaline isolated then being optically inactive. This does not necessarily support formula (I) for the structure of the glyoxaline since experiment showed that optically active benzoin is slowly racemised at room temperature and more quickly at the boiling point in glacial acetic acid solution. The mechanism of formation of the glyoxaline is depicted conveniently by utilising the stilbenediol form of benzoin.



and this form has also been used extensively to explain the catalytic racemisation of optically active benzoins and related compounds (see Roger and McGregor, *J.*, 1934, 1545). More

* Part X, *J.*, 1954, 811.

important and convincing experimental evidence in favour of this mechanism is now adduced in the following facts. We had hoped to realise the synthesis of optically active glyoxalines [*e.g.* (III) and (IV)] thus :

and, moreover, optically active ethylbenzoins had already been prepared in these laboratories (McKenzie and Ritchie, *Ber.*, 1937, **70**, 23; Roger, *J.*, 1937, 1048; 1939, 108). However, the condensation of *rac.*-ethylbenzoin and urea under even more drastic conditions than those recorded for benzoins and urea failed completely, most of the ketol being recovered unchanged. Similar lack of success attended the use of phenylbenzoin. Ketols such as ethylbenzoin offer no possibility of change into isomeric dienolic forms such as are possible with benzoin and, furthermore, the optically active forms are not susceptible to catalytic racemisation with alkali. These results support the foregoing mechanism for the formation of dihydro-oxodiphenylglyoxaline and formula (I) as its probable structure.

Stilbenediol diacetate (Barnes and Tulane, *J. Amer. Chem. Soc.*, 1940, **62**, 896) and urea in boiling glacial acetic acid yielded no dihydro-oxo-4 : 5-diphenylglyoxaline but only unidentified products. Perchance, glacial acetic acid may not be the proper condensing agent in this case. We found that desyl chloride and urea in boiling acetic acid did yield small amounts of the glyoxaline, but once again the main products were unidentified solids.

Experimental

2 : 3-*Dihydro*-2-*oxo*-4 : 5-*diphenylglyoxaline* (cf. Biltz, *Annalen*, 1905, **339**, 265; *Org. Synth.*, 1932, **12**, 34). *rac.*-Benzoin (32 g.) and urea (11 g., 1·85 mols.) were refluxed in glacial acetic acid (80 c.c.) for 7 hr. The crystals which separated on cooling were filtered off, washed with ether, and crystallised from glacial acetic acid; the product (22·1 g.) had m. p. 325—328°.

Attempted Preparation of Optically Active 2 : 3-*Dihydro*-2-*oxo*-4 : 5-*diphenylglyoxaline*.—(+)-Benzoin (3·6 g; $[\alpha]_{5461}^{20}$ +144·0° in acetone) and urea (1·75 g., 1·85 mols.) yielded a product (3·25 g.), m. p. 324—326°, identical with the compound obtained above.

Condensation of Stilbenediol Diacetate and Urea.—The diacetate (0·65 g.) (Barnes and Tulane, *loc. cit.*) and urea (0·25 g., 1·8 mols.) were refluxed for 6½ hr. in glacial acetic acid (2·5 c.c.). A white unidentified solid (0·4 g.), m. p. 200—203°, separated on cooling. No other product was isolated.

Condensation of rac.-*Desyl Chloride and Urea.*—*rac.*-Desyl chloride (5·5 g.) and urea (2·6 g., 1·8 mols.) were refluxed in glacial acetic acid (20 c.c.) for 6 hr. Ammonium chloride (0·5 g.) separated on cooling, and on dilution of the liquors with water 2 : 3-dihydro-2-oxo-4 : 5-diphenylglyoxaline (0·4 g.), m. p. 330—333°, was precipitated. An ether extract of the dilute acid liquors yielded a small amount of unidentified yellow crystals, m. p. 213—214°. On neutralisation of the acid liquors with sodium hydrogen carbonate an unidentified solid, m. p. 243—245°, separated.

Attempted Condensation of rac.-*Ethylbenzoin and Urea.*—*rac.*-Ethylbenzoin (4·8 g.) and urea (2·2 g., 1·8 mols.) were refluxed for 30 hr. in glacial acetic acid (16 c.c.). Unchanged *rac.*-ethylbenzoin (4·5 g.), m. p. 65—70°, slowly separated from the liquors on cooling.

Attempted Condensation of Phenylbenzoin and Urea.—Phenylbenzoin (0·4 g.), m. p. 80—82°, was recovered unchanged after glacial acetic acid (2 c.c.), urea (0·21 g., 1·8 mols), and *rac.*-phenylbenzoin (0·55 g., 1 mol.), m. p. 83—84°, had been refluxed for 16 hr.

Racemisation of (+)-*Benzoin in Glacial Acetic Acid.*—(+)-Benzoin (1 g.; $[\alpha]_{5461}^{20}$ +144·6° in acetone) was dissolved in glacial acetic acid (30 c.c.), and the solution halved ($l = 0·5$, $c = 3·3$ for all readings). (i) One half was kept at room temperature, and rotations (all positive) were read every few days :

Time, days ...	0	1	2	5	12	21	30	40	55	70	500
α_{5461}^{20}	4·52°	4·48°	4·45°	4·33°	4·14°	3·99°	3·68°	2·88°	2·01°	1·27°	1·12°
$[\alpha]_{5461}^{20}$	273·9°	271·5°	269·8°	262·4°	250·9°	241·8°	223·0°	174·6°	121·8°	96·8°	67·9°

The (+)-benzoin recovered from the liquors had m. p. 127—128°, $[\alpha]_{5461}^{20}$ +93·58° in acetone, after one crystallisation from ethyl alcohol.

(ii) The other half was boiled for several hours, the optical rotation (positive) being read every hour :

Time of boiling, hr.	*	1	2	3	4	5	6
α^{20}_{5461}	4·3°	2·38°	0·58°	0·26°	0·17°	0·17°	0·17°
$[\alpha]^{20}_{5461}$	260·6°	144·2°	35·15°	15·76°	10·3°	10·3°	10·3°

* Time required for solution to be heated to the b. p.

The partially racemised (+)-benzoin recovered from the liquors had m. p. 129—130°, $[\alpha]^{20}_{5461}$ +10·1° (in acetone), after one crystallisation from ethyl alcohol. A small amount of benzil, m. p. 94—95°, was also recovered.

We thank the Carnegie Trust for the Universities of Scotland and the Department of Scientific and Industrial Research for the support which made this work possible.

UNIVERSITY COLLEGE, DUNDEE, UNIVERSITY OF ST. ANDREWS. [*Received, May 11th,* 1953.]

Calculations on the Electronic Spectra of trans-*Butadiene by a Semi-empirical Molecular-orbital Approximation.*

By CARL M. MOSER.

[Reprint Order No. 5349.]

Calculations on the lowest electronic transitions of *trans*-butadiene have been carried out within the framework of a semi-empirical molecular-orbital approximation recently proposed by Pariser and Parr. The " best " possible wave functions for the molecule predict values of the energy and intensity of transitions that are in satisfactory agreement with experimental results. The problem of choosing the most significant configurations to build a good, approximate wave function is discussed. Finally, a comparison is made between the use of arbitrary molecular orbitals and self-consistent field (SCF) molecular orbitals as the starting point for the calculations.

ONE of the interesting possibilities for the use of a semi-empirical molecular-orbital approximation recently proposed by Pariser and Parr (*J. Chem. Phys.*, 1953, **21**, 466, 767; cf. Pople, *Trans. Faraday Soc.*, 1953, **49**, 1375) appears to be in the study of the molecular properties of large molecules in a more satisfactory manner than has yet been possible. Heretofore, there has been only a very limited application of the non-empirical anti-symmetrized molecular orbital (ASMO) approximation, including configuration interaction (CI), to molecules of even moderate size such as naphthalene (*e.g.*, Jacobs, *Proc. Phys. Soc.*, 1948, **62**, *A*, 710). This has been largely due to the very tedious algebra necessary in calculations of the matrix elements, although it is now likely that electronic computers could aid in avoiding a considerable portion of the labour. For the smaller molecules, for which it has been possible to construct the best possible wave functions within the framework of the non-empircal ASMO–CI approximation, the accord between the predictions of the calculations and the experimental observations on electronic spectra often leaves much to be desired. The order of excited levels may not be the same, or, in those cases where there is agreement as to the order, the calculated and the observed transition energies may differ by several electron-volts.

The results published so far (Pariser and Parr, *loc. cit.*) on the application of the semi-empirical approximation to some hydrocarbons and heteromolecules give satisfactory agreement between calculation and experiment, although for each example wave functions have been built from a superposition of only a few of the total possible number of configurations. Before one can definitely assess the value of this approximation, it will be necessary to consider one molecule in rather greater detail than has been done up to now.

Pariser and Parr have reported partial calculations on butadiene (utilizing 3 of the possible 12 configurations for the ground state, and 2 of the possible 8 configurations for the excited state) and the accord between experiment and calculation on the energy and order of electronic transitions is satisfactory. As a model and guide to calculations for

large molecules we now expand these calculations. Specifically, we shall be interested in four aspects of the calculations on ultra-violet spectra: (1) Using the ASMO non-empirical approximation and starting either with Hückel or SCF orbitals, single configuration calculations on the electronic spectra of butadiene are in qualitative agreement with the observed order of transition (*i.e.*, an allowed transition followed by a forbidden transition) although the predicted energies are 2—3 ev larger than the excitations observed. However, when nearly the " best " possible wave functions, obtained from the CI procedure, are used, the order of calculated transition changes so that the forbidden should be of lower energy than the allowed transition (Lefebvre, Ph.D. Thesis, London, 1953; Pullman and Baudet, *Compt. rend.*, 1954, **238**, 241). It will be of interest to know whether a similar crossing of the lowest excited levels occurs in this semi-empirical approximation when the " best " wave functions are used. (2) The identification of transitions will be more secure if a quantitative comparison of observed and calculated intensities is made in addition to a comparison of transition energies. Pariser and Parr's calculations give no information on this point. (3) Even by using an electronic calculator it will, in general, for the larger molecules, not be possible to build up the state wave functions from all possible configurations. We shall discuss some arbitrary methods of choosing the most important configurations. (4) Linked with (3) is the difficult problem of choosing the set of molecular orbitals with which to commence calculation. To illustrate this point, a comparison will be made between an arbitrary set of orbitals and the SCF molecular orbitals, which are found within the framework of the semi-empirical approximation.

Calculations.—The details of the method of calculation have been given by Pariser and Parr. *trans*-Butadiene will be assumed to have the following form:

$$C_{(1)}—C_{(2)}\diagup\!\!\diagdown C_{(3)}—C_{(4)}$$

with $C_{(1)}$–$C_{(2)} = 1{\cdot}35$ Å, $C_{(2)}$–$C_{(3)} = 1{\cdot}46$ Å, and $\angle C_{(1)}C_{(2)}C_{(3)} = 124°$ (Shomaker and Pauling, *J. Amer. Chem. Soc.*, 1939, **61**, 1769): it is, of course, planar. Only the four $2p\pi$ electrons will be considered explicitly; the $2p\sigma$ electrons are considered only as they furnish a potential field in which the π electrons move. For the four electrons four molecular orbitals can be written, and the orthonormal set suggested by Parr and Pariser will be used. In order of increasing energy, they are:

		Symmetry (point group C_{2h})	
ϕ_K	$= \frac{1}{2}(\chi_1 + \chi_2 + \chi_3 + \chi_4)$	a_u	
ϕ_L	$= \frac{1}{2}(\chi_1 + \chi_2 - \chi_3 - \chi_4)$	b_g	. . . . . (1)
ϕ_M	$= \frac{1}{2}(\chi_1 - \chi_2 - \chi_3 + \chi_4)$	a_u	
ϕ_N	$= \frac{1}{2}(\chi_1 - \chi_2 + \chi_3 - \chi_4)$	b_g	

The symmetry symbols of lower-case letters refer to the symmetry of the individual molecular orbitals; the symmetry symbols of capital letters refer to the symmetry of configurations. It may be well to recall that $a_u \times b_g = B_u$, $a_u \times a_u = A_g$, and $b_g \times b_g = A_g$.

These particular molecular orbitals have been chosen in this instance because they are convenient mathematically. As the state functions will be built from a linear combination of " all possible " configurations, algebraic convenience is sufficient reason. Pariser and Parr pointed out that these orbitals would probably be close to the SCF orbitals and that is, in fact, so (see below).

By distributing the four electrons in the four molecular orbitals it would be possible to write 70 independent wave functions. The problem will be simplified by considering only the singlet states, as the triplet state of butadiene does not appear, as yet, to have been accurately observed.

It will be desirable to have a simple notation to indicate the space co-ordinates of the configurations. For example, K^2L^2 will indicate the configuration in which there are two electrons in ϕ_K and two in ϕ_L. The determinantal wave function can be written as:

$$\psi_{K^2L^2} = (4!)^{-\frac{1}{2}} \det.|\phi_K(1)\alpha(1)\ \phi_K(2)\beta(2)\ \phi_L(3)\alpha(3)\ \phi_L(4)\beta(4)| \equiv |\phi_K\bar{\phi}_K\phi_L\bar{\phi}_L| \quad . \quad (2)$$

For one electron in each of two molecular orbitals, either a singlet or triplet can be written and only the former will be considered here:

$$\psi_{K\cdot LM} = (2)^{-\frac{1}{2}}\{|\phi_K\overline{\phi}_K\phi_L\overline{\phi}_M| - |\phi_K\overline{\phi}_K\overline{\phi}_L\phi_M|\} \quad . \quad . \quad . \quad . \quad . \quad (3)$$

When there is one electron in each of the four molecular orbitals some difficulty will arise, for then two singlets can be written for this distribution. If these are taken to be of the same form as Coulson and Jacobs (*Proc. Roy. Soc.*, 1951, *A*, **206**, 281) used for butadiene:

$$\psi^a{}_{KLMN} = \tfrac{1}{2}\{|\phi_K\overline{\phi}_L\phi_M\overline{\phi}_N| - |\overline{\phi}_K\phi_L\phi_M\overline{\phi}_N| - |\phi_K\overline{\phi}_L\overline{\phi}_M\phi_N| + |\overline{\phi}_K\phi_L\overline{\phi}_M\phi_N|\} \quad . \quad (4)$$

$$\psi^b{}_{KLMN} = \tfrac{1}{2}\{|\phi_K\overline{\phi}_L\phi_M\overline{\phi}_N| - |\phi_K\phi_L\overline{\phi}_M\overline{\phi}_N| - |\overline{\phi}_K\overline{\phi}_L\phi_M\phi_N| + |\overline{\phi}_K\phi_L\overline{\phi}_M\phi_N|\} \quad . \quad (5)$$

it will be observed that expressions (4) and (5) are not orthogonal. It will be convenient to take the following linear combinations that are:

$$\psi^A{}_{KLMN} = (\psi^a{}_{KLMN} + \psi^b{}_{KLMN})/\sqrt{3} \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

$$\psi^B{}_{KLMN} = (\psi^a{}_{KLMN} - \psi^b{}_{KLMN}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

In only one unimportant detail do the calculations reported here differ from those carried out by Pariser and Parr. Here, all effect of the hydrogen atoms in the molecule will be ignored. In substance, this results in a change of their formula for α_p to:

$$\alpha_p = W_{2p} - \sum_{p \neq q}[(pp|qq) + (q:pp)] \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

where the notation is that used by Pariser and Parr. This has been done to make more meaningful a comparison between these calculations and non-empirical ASMO–CI calculations where all effect of the hydrogen atoms was neglected. It will now be necessary to give an explicit value to $(q:pp)$, which has been assumed to have an average value of 0·6 ev for nearest neighbours and 0·1 ev for next-nearest neighbours. The value of $(q:pp)$ for $C_{(1)}$–$C_{(2)}$ should, of course, be somewhat larger than for $C_{(2)}$–$C_{(3)}$, but it will probably introduce only a negligible error in the calculation to take an average value. The values of other atomic integrals have been given by Pariser and Parr. It should be mentioned that whether one calculates α as Pariser and Parr have done or by equation (8), it will not affect the value of the empirical parameters β or the diagonal elements of the matrix; it will, however, make some difference in a few of the non-diagonal elements.

Within the framework of this semi-empirical approximation it is possible to calculate the SCF molecular-orbitals for butadiene. Pople (*loc. cit.*) has given the general formulæ for the calculation of the eigenfunctions of the Hartree–Fock operator (cf. Roothann, *Rev. Modern Phys.*, 1951, **23**, 69; Parr and Mulliken, *J. Chem. Phys.*, 1950, **18**, 1338; Coulson and Jacobs, *loc. cit.*) and has calculated the orbitals for the ground state of butadiene for a semi-empirical approximation similar to that used in this paper. The exact value of the orbitals will depend on the precise details of the computation. The equations (9) differ slightly from those given by Pople:

$$\begin{aligned}
\phi_k &= 0{\cdot}426(\chi_1 + \chi_4) + 0{\cdot}564(\chi_2 + \chi_3) \\
\phi_l &= 0{\cdot}536(\chi_1 - \chi_4) + 0{\cdot}461(\chi_2 - \chi_3) \\
\phi_m &= 0{\cdot}564(\chi_1 + \chi_4) - 0{\cdot}426(\chi_2 + \chi_3) \\
\phi_n &= 0{\cdot}461(\chi_1 - \chi_4) - 0{\cdot}536(\chi_2 - \chi_3)
\end{aligned} \quad . \quad . \quad . \quad . \quad . \quad (9)$$

To distinguish these SCF molecular orbitals from the arbitrary molecular orbitals used in expression (1), lower-case indices k, l, m, n are used here.

The results of the calculations are gathered in the several tables. In Table 1 the data for the wave function for the ^1A_g state that can be obtained from a consideration of all possible configurations of this symmetry have been summarized. In columns (*a*) are listed the space co-ordinates of the configurations, in (*b*) the energy of the configurations relative to the lowest configuration before CI, in (*c*) the energy of the one or two lowest configur-

ations after CI, in (*d*) the weight, *i.e.*, the square of the coefficient, of that configuration in the total wave function, and in (*e*) the lowering of the lowest configuration by the configuration in question calculated by second-order perturbation theory. This has been done by the usual formula:

$$H_{oi}^2/(H_{ii} - H_{oo}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

where the index o refers to the lowest configuration and i refers to any other configuration. The starting molecular orbitals for the calculations of this and the next four Tables have been the functions (1).

Table 2 lists similar data for the eight possible configurations in the ^1B_u state.

In Table 1 it will be observed that there are three configurations for which the second-order perturbation theory gives a lowering of zero, which is to say that as a first approximation the effect of these configurations in the total wave function should be very small. In Table 3 are collected the data for the ^1A_g state when only the nine mono- and di-excited configurations are considered as contributing to the wave function.

Tables 4 and 5 are more restrictive, considering only the mono-excited configurations as making a contribution to the ^1A_g and the ^1B_u state respectively.

TABLE 1. ^1A_g *state of butadiene* (12 *configurations*).

(*a*)	(*b*) (ev)	(*c*) (ev)	(*d*)	(*e*) (ev)	(*a*)	(*b*) (ev)	(*c*) (ev)	(*d*)	(*e*) (ev)
K^2L^2	0·00	−0·77	0·927	—	KMN^2 ...	19·35	—	0·000	0·000
K^2M^2	10·24	—	0·010	0·056	K^2LN	7·67	—	0·004	0·075
K^2N^2	13·70	—	0·003	0·049	LM^2N ...	19·35	—	0·000	0·000
L^2M^2	13·70	—	0·002	0·049	$KLMN^A$ ...	16·14	—	0·011	0·107
L^2N^2	16·96	—	0·002	0·034	$KLMN^B$ ...	14·32	—	0·006	0·053
M^2N^2	23·36	—	0·000	0·000					
KL^2M ...	7·67	+6·50	0·035	0·337				Total	0·76

TABLE 2. ^1B_u *state of butadiene* (8 *configurations.*)

(*a*)	(*b*) (ev)	(*c*) (ev)	(*d*)	(*e*) (ev)	(*a*)	(*b*) (ev)	(*c*) (ev)	(*d*)	(*e*) (ev)
K^2LM ...	5·88	5·68	0·967	—	KLN^2	17·11	—	0·002	0·016
LMN^2 ...	20·92	—	0·003	0·038	KL^2N	9·25	—	0·012	0·020
L^2MN ...	17·11	—	0·000	0·016	KM^2N ...	17·56	—	0·004	0·043
K^2MN ...	12·07	—	0·002	0·002					
KLM^2 ...	13·75	—	0·009	0·064				Total	0·199

TABLE 3. ^1A_g *state of butadiene* (9 configurations).

(*a*)	(*b*) (ev)	(*c*) (ev)	(*d*)	(*e*) (ev)	(*a*)	(*b*) (ev)	(*c*) (ev)	(*d*)	(*e*) (ev)
K^2L^2	0·00	−0·76	0·929	—	KL^2M ...	7·67	+6·58	0·035	0·337
K^2M^2	10·24	—	0·009	0·056	K^2LN	7·67	—	0·005	0·075
K^2N^2	13·70	—	0·003	0·049	$KLMN^A$ ...	16·14	—	0·010	0·107
L^2M^2	13·70	—	0·002	0·049	$KLMN^B$ ...	14·32	—	0·005	0·053
L^2N^2	16·96	—	0·002	0·034					
								Total	0·76

TABLE 4. ^1A_g *state of butadiene* (3 *configurations*).

(*a*)	(*b*) (ev)	(*c*) (ev)	(*d*)	(*e*) (ev)
K^2L^2	0·00	−0·39	0·955	—
KL^2M ...	7·67	7·55	0·038	0·337
K^2LN	7·67	—	0·008	0·075
			Total	0·412

TABLE 5. ^1B_u *state of butadiene* (3 *configurations*).

(*a*)	(*b*) (ev)	(*c*) (ev)	(*d*)	(*e*) (ev)
K^2LM ...	5·88	5·81	0·990	—
KLM^2 ...	13·75	—	0·010	0·064
K^2MN ...	12·07	—	0·001	0·002
			Total	0·066

(For meanings of *a*—*e* see text.)

There would be no point in calculating the best wave functions using the SCF orbitals (9) as the result would, of course, be the same as that previously found. It has been thought of interest to calculate the relative energies of the configurations and the approximate

lowering of the lowest configuration as calculated by second-order perturbation theory. These results are collected in Tables 6 and 7 for the ^1A_g and the ^1B_u state respectively.

TABLE 6. ^1A_g *state of butadiene* (*calculated from SCF orbitals*).

(*a*)	(*b*) (ev)	(*c*) (ev)	(*a*)	(*b*) (ev)	(*c*) (ev)	(*a*)	(*b*) (ev)	(*c*) (ev)
k^2l^2	0·00	—	l^2n^2.....	17·12	0·024	$klmn^A$	16·51	0·082
k^2m^2	10·73	0·095	kl^2m	7·85	0·000	$klmn^B$	14·56	0·051
k^2n^2	13·84	0·046	k^2ln	7·68	0·000			
l^2m^2	14·46	0·039					Total	0·337

TABLE 7. ^1B_u *state of butadiene* (*calculated from SCF orbitals for* ^1A_g *state*).

(*a*)	(*b*) (ev)	(*c*) (ev)	(*a*)	(*b*) (ev)	(*c*) (ev)	(*a*)	(*b*) (ev)	(*c*) (ev)
k^2lm	6·39	—	k^2mn	13·98	0·017	kl^2n	9·23	0·040
lmn^2	21·74	0·028	klm^2	14·19	0·051	km^2n	18·18	0·028
l^2mn	17·49	0·029	kln^2	17·08	0·000			
							Total	0·193

Discussion.—In Table 8 are summarized the data on the electronic spectra. In column (*a*) are the experimental results; other columns give the results of calculations using (*b*) the best wave functions of Tables 1 and 2, (*c*) the approximate function of Table 3 for the ^1A_g state, (*d*) the mono-excited configurations of Tables 4 and 5, (*e*) the lowest configurations [starting with equations (1)], (*f*) the lowest configurations starting with the SCF orbitals (9), and (*g*) the lowest configurations starting with the non-empirical SCF orbitals; for (*h*) calculations were used similar to those for (*c*) in the ASMO–CI approximation.

The *f* values in (*a*)—(*f*) have been calculated by using the computed value of the excitation energy. For consistency with the fundamental assumptions of the approximation, all cross-terms have been neglected. In (*g*) and (*h*) it is not clear what value (computed or experimental) of the transition energy has been used.

First, it is observed that the agreement between (*a*) and (*b*) is very satisfactory. This suggests that if it were possible to use the best wave functions in this semi-empirical scheme, the value of the predictions should be reasonably significant. Unfortunately, in practice it will not be possible to construct the best wave functions for large molecules even by using an electronic computer. It will always be necessary to attempt to choose the most significant configurations so as to approximate satisfactorily to the best wave function. Some possible approximations are columns (*c*)—(*f*). The agreement between (*a*) and (*c*) is also satisfactory, and the difference between (*b*) and (*c*) is not very large. If it should be generally true that one can neglect all configurations which differ from the lowest configuration by more than two orbitals, then the enormously tedious problem of CI would be reduced to a scale that an electronic computer might be able to handle in a fairly complete manner. The three configurations in Table 1 for which the second-order perturbation-theory lowering is zero might have been excluded from the calculation on the grounds that the energies of these configurations are so high (~20 ev above the lowest configuration) that the whole approximation of CI breaks down. Whether one is justified in doing this depends somewhat on whether one thinks of CI as being a purely mathematical procedure or whether one assumes that the configurations must have some physical reality, at least to the extent of not appearing in the continuum.

The comparison between (*a*), (*c*), and (*h*) is interesting for here one observes how slightly reliable even very detailed non-empirical calculations can be. The reasons for this are not entirely clear at present, but at least some of the contributing factors are understood. Briefly, the calculated value of the one-centre, two-electron atomic integral is much too large (Moffitt, *Proc. Roy. Soc.*, 1950, *A*, **202**, 534; Pariser, *J. Chem. Phys.*, 1953, **21**, 568) and it seems likely other Coulomb integrals calculated from Slater-type functions are somewhat too large (Pariser and Parr, *loc. cit.*). One cannot follow Pullman and Baudet (*loc. cit.*) in suggesting that the difficulty in butadiene is due to the poor approximation to the ^1B_u wave function. As they included all eight configurations in this calculation, they arrived of necessity at the " best possible " wave function for this state.

The good agreement between (*a*) and (*d*) suggests at first sight that it might be possible to use the lowest configuration and just mono-excited configurations to build a reasonably satisfactory wave function. This possibility, however, needs to be examined with caution. It can be shown (Lefebvre, *Compt. rend.*, 1953, **237**, 1158) that, if one builds configurations from the SCF orbitals for that particular state, the matrix elements between the lowest configuration and mono-excited configurations are zero, while the matrix elements between the lowest configuration and di-excited configurations are not zero. However, if the configurations are constructed from orbitals other than the SCF orbitals, both these matrix elements are usually non-zero and experience in this semi-empirical approximation seems to indicate that the lowering of the lowest configuration by mono-excited configurations (as calculated by second-order perturbation theory) is likely to be greater than that by the di-excited configurations. In a sense, then, the mono-excited are " more important " than the di-excited configurations. One would prefer, of course, to build the wave functions for states from all the important mono- and di-excited configurations, or, alternatively, to start from the SCF orbitals and use the important di-excited configurations. Both these objectives will, unfortunately, be impracticable for many molecules. In such instances, using just the lowest plus mono-excited configurations may lead to a fairly good approximate wave function, though possibly not one better than would have resulted from building only single configurations from the SCF orbitals.

The agreement between (*a*) and (*e*) in Table 8 is also good, but this, particularly with regard to the *f* values, must be considered somewhat fortuitous. The agreement between (*a*) and (*f*) is satisfactory as regards order and energy of transitions but, unfortunately, the calculated intensity is nearly twice that observed. This is disappointing, for the SCF orbitals in this approximation (at least for the ground state) are not difficult to calculate, and, if single configuration calculation had given good agreement for both energy and intensity, much of the difficulty associated with wave-mechanical calculations might have been avoided.

TABLE 8. *Electronic transition energies* (eV) *for* trans-*butadiene.*

Transition :	(*a*) [1]	(*b*)	(*c*)	(*d*)	(*e*)	(*f*)	(*g*) [2, 3]	(*h*) [2, 3]
$^1A_g \longrightarrow {}^1B_u$ ...	6·0	6·45	6·44	6·20	5·88	6·39	8·1	9·6
f value	0·53	0·51	0·51	0·51	0·47	0·93	1·05	0·44
$^1A_g \longrightarrow {}^1A_g$ ...	7·2	7·27	7·34	7·94	7·67	7·68	10·1	7·1

[1] Mulliken, *Rev. Modern Phys.*, 1942, **14**, 265. [2] Lefebvre, *loc. cit.* [3] Pullman and Baudet, *loc. cit.*

The rather large difference in the calculated *f* values of (*e*) and (*f*), while the energies calculated are not very different, is expected. It is well known that *f* values are extremely sensitive to the form of the wave function and, although (1) and (9) are reasonably close together, the small difference between these would be magnified in the calculated *f* values. It is also well known that the energies associated with rather different wave functions may not differ very much. It might be tempting to suppose that the satisfactory qualities of the arbitrary molecular orbitals (1) have some general applicability. The same general form of the orbitals (1) have been applied to calculations on naphthalene, and the resulting configurations do not separate nearly as well as those reported here for butadiene. We hope to present some details of these calculations later.

It is now well known that the SCF single configuration is not an exact eigenfunction of the many-electron Hamiltonian, as with a single configuration one has as yet to account for the energy of correlation of electrons of opposite spin. Lefebvre (*loc. cit.*) has made a careful study of this for butadiene in the ASMO–CI approximation, using the SCF orbitals for the ^1A_g state, and has found that the energy of correlation is fairly considerable, about 2·2 ev. As will be observed from Table 6 this energy is approximated by second-order perturbation theory, which we have seen is likely to be reasonably accurate from Tables 1—5 and to be about 0·3 ev. It appears that the lowering from the analytically computed value of most of the coulomb-type atomic integrals has to a large extent accounted for the correlation energy.

Most of the conclusions that we have reached from studying Tables 1—5 are due to the coincidence that the orbitals (1) are reasonably close to the SCF orbitals (9). From this it

has followed that, by the assumptions of this semi-empirical approximation, the configurations are very largely independent of one another. CI is not of primary importance, as in the ASMO–CI approximation, and second-order perturbation theory affords a reasonably good approximation. The emergence of the independenc of configurations may well prove to be one of the most important advantages of the present theory (these advantages are also to be found in Moffitts's theory of " atoms in molecules," *Proc. Roy. Soc.*, 1951, *A*, **210**, 245, and later papers, although it does not now seem likely that this theory can be applied in practice to very large molecules). It may be well to emphasize that this independence probably does not hold if the starting orbitals are very far from the SCF orbitals.

The eigenvalues and eigenvectors of the CI matrices (with the exception of Tables 6 and 7) were determined on ACE at the National Physical Laboratory, Teddington, through the kind co-operation of Dr. J. H. Wilkinson. The author is pleased to acknowledge his indebtedness to Dr. Roland Lefebvre for many stimulating discussions and to Dr. R. Daudel for reading the manuscript. This work has been supported by a grant from the U.S. Public Health Service.

PAVILLON PASTEUR, INSTITUT DU RADIUM, PARIS, 5. [*Received, May 3rd,* 1954.]

---

1 : 2 : 4-*Triazoles. Part I. A Synthesis of* 3 : 5-*Disubstituted* 1 : 2 : 4-*Triazoles.*

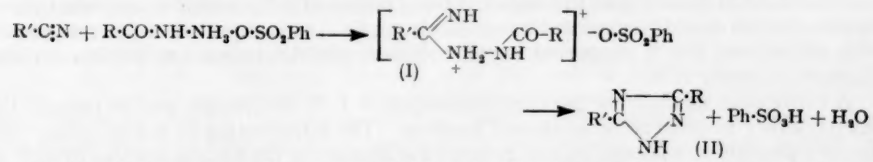
By K. T. POTTS.

[Reprint Order No. 5363.]

The reaction of benzhydrazide benzenesulphonate or *p*-nitrobenzhydrazide benzenesulphonate with various aromatic cyanides results in the formation of 3 : 5-diaryl-1 : 2 : 4-triazoles.

OXLEY and SHORT (*J.*, 1946, 147) established a new method for the preparation of amidines and their *N*-monosubstituted derivatives by heating the ammonium or alkyl- or aryl-ammonium salt of an aromatic or aliphatic sulphonic acid with a cyanide at high temperatures. The present paper describes an application of their method to the preparation of 3 : 5-diaryl-1 : 2 : 4-triazoles by heating an unsubstituted acylhydrazide benzene- or toluene-*p*-sulphonate with an aromatic cyanide at 200—250°. Cyanides have been used previously to obtain sodio-derivatives of amidines by reaction with an aromatic amine in the presence of sodium (von Walther, *J. prakt. Chem.*, 1894, **50**, 91; von Walther and Grossmann, *ibid.*, 1908, **78**, 478; Engelhardt, *ibid.*, 1896, **54**, 143) and, when two molecules of the cyanide and one molecule of phenylhydrazine reacted in the presence of sodium, a 1 : 2 : 4-triazole was formed. Atkinson and Polya (*J.*, 1952, 3418) were unable to effect condensation of a nitrile with a benzhydrazide under the conditions employed by Pellizzari (*Gazzetta*, 1911, **41**, II, 20) and they are of the opinion that the low yields obtained from such condensations are due to the formation of nitriles.

It is most likely that the reaction may be represented by the following stages:



The identity of the product was established by direct comparison (m. p., mixed m. p., and infra-red spectrum; picrate and acetyl derivative) with an authentic specimen prepared by Pellizzari's method. This method for the preparation of triazoles has been restricted to the use of aromatic cyanides, and the results are shown in the Table. Further applications of this method are being studied. The influence of reaction conditions has

not been thoroughly investigated, so that the recorded yields (of crude material) are not necessarily the highest obtainable. The method has the advantage of being a one-stage process which can be operated without employing a solvent. In common with other similar systems containing an imino-group triazoles are weakly acidic and form salts with metals; use is made of this property in the isolation and purification.

The triazole (II; R = Ph, R′ = *p*-C_6H_4·NO_2) obtained from the condensation of *p*-nitrophenyl cyanide and benzhydrazide benzenesulphonate was identical with that obtained from phenyl cyanide and the corresponding *p*-nitrobenzhydrazide benzenesulphonate. The fact that only one form was isolated supports the hypothesis that a true tautomeric system is present in the triazole nucleus for otherwise two isomers would be expected. The ultra-violet absorption spectra of several of these triazoles have been determined but they fail to exhibit any selective absorption other than that due to the phenyl nucleus. In the infra-red spectrum the presence of a highly associated imino-group is indicated, and 3 : 5-diphenyl-1 : 2 : 4-triazole and 3-phenyl-5-*p*-tolyl-1 : 2 : 4-

TABLE 1. 3-R^1-5-R^2-1 : 2 : 4-*triazoles.*

R^1	R^2	M. p.	Yield, %	Formula	Found, % C	Found, % H	Found, % N	Reqd., % C	Reqd., % H	Reqd., % N	
Ph	Ph	190°	92	$C_{14}H_{11}N_3$	76·1	5·0	18·9	76·0	5·0	19·0	[a]
Ph	*p*-C_6H_4Me	189	quant.	$C_{15}H_{13}N_3$	76·3	5·9	17·8	76·6	5·6	17·9	[b]
Ph	*o*-C_6H_4Me	—	—	—	—	—	—	—	—	—	[c]
Ph	α-$C_{10}H_7$	118	88	$C_{18}H_{13}N_3$	78·8	5·1	15·9	79·7	4·8	15·5	[d]
Ph	*p*-C_6H_4·NO_2	239	quant.	$C_{14}H_{10}O_2N_4$	62·5	3·9	21·2	63·1	3·8	21·0	[e]
p-C_6H_4·NO_2	Ph	240	86	$C_{14}H_{10}O_2N_4$	63·2	3·9	20·6	63·1	3·8	21·0	[e]
p-C_6H_4·NO_2	*p*-C_6H_4Me	244	quant.	$C_{15}H_{12}O_2N_4$	64·6	4·6	20·4	64·3	4·3	20·0	[f]
p-C_6H_4·NO_2	CH_2Ph	212	84	$C_{15}H_{12}O_2N_4$	64·6	4·5	20·3	64·3	4·3	20·0	[g]
p-C_6H_4·NO_2	*p*-C_6H_4·NO_2	250—251	58	$C_{14}H_{10}O_4N_5$	54·1	3·2	22·5	54·0	2·9	22·5	[h]
p-C_6H_4·NO_2	α-$C_{10}H_7$	192	80	$C_{18}H_{12}O_2N_4$	68·5	4·0	17·5	68·4	3·8	17·7	[i]
α-C_5H_4N	Ph	212	86	$C_{13}H_{10}N_4$	70·0	4·7	25·3	70·3	4·6	25·1	[j]
α-C_5H_4N	*p*-C_6H_4Me	202	77	$C_{14}H_{12}N_4$	71·2	5·3	23·8	71·1	5·1	23·7	[k]

[a] Needles from light petroleum. [b] Needles from light petroleum. *Picrate*, brilliant yellow needles, m. p. 156°, from benzene (Found: C, 60·0; H, 4·3; N, 16·1. $C_{21}H_{16}O_7N_6$,C_6H_6 requires C, 59·8; H, 4·1; N, 15·5%). N-*Acetyl* derivative, needles, m. p. 93°, from light petroleum (Found: C, 74·0; H, 5·6; N, 14·9. $C_{17}H_{15}ON_3$ requires C, 73·6; H, 5·5; N, 15·2%). [c] Isolated as the *picrate*, yellow needles, m. p. 176°, from aqueous alcohol (Found: C, 51·5; H, 3·9. $C_{21}H_{16}O_7N_6$,1·5H_2O requires C, 51·3; H, 3·9%). The water was not lost on drying, and the infra-red spectrum indicated the presence of a highly-bonded hydroxyl group. [d] Long needles from light petroleum. Analytical results obtained for carbon were always low. *Picrate*, irregular, yellow prisms, m. p. 206°, from methanol (Found: C, 57·5; H, 3·3. $C_{24}H_{16}O_7N_6$ requires C, 57·6; H, 3·2%). [e] Needles from light petroleum. These two compounds were identical in m. p., mixed m. p., and infra-red spectra. [f] Fluffy needles from light petroleum. [g] Plates from light petroleum. [h] Fawn needles from aqueous alcohol. [i] Glistening fawn needles from aqueous alcohol. [j] Needles from aqueous alcohol. *Picrate*, small, yellow needles, m. p. 201°, from benzene (Found: C, 50·7; H, 3·2; N, 21·5. $C_{19}H_{13}O_7N_7$ requires C, 50·6; H, 2·9; N, 21·7%). [k] Cubes from light petroleum. *Picrate*, yellow needles, m. p. 194°, from alcohol (Found: N, 20·9. $C_{20}H_{15}O_7N_7$ requires N, 21·1%).

triazole show this effect very strongly. Molecular-weight determinations, however, yield normal results. It is quite possible that the tautomeric nature of the triazoles might be due to such an interaction between two or more molecules and not involve the shift of hydrogen from one nitrogen to another. In the corresponding *N*-acetyl-1 : 2 : 4-triazoles no imino-band is present and the carbonyl band occurs at 5·7 μ which is somewhat lower than that which would be expected for an amide group. As is expected, little or no association occurs and this is supported by molecular-weight determinations (cf. Hunter and Marriott, *J.*, 1941, 777).

A convenient method for the characterization of 1 : 2 : 4-triazoles was to prepare the picrate, either in benzene or in alcohol solution. The introduction of a nitro-group into the *para*-position of a phenyl nucleus reduced the basicity of the triazole nucleus to such an extent that the corresponding picrates could not be isolated in a pure condition. In the glyoxaline series the direct introduction of a nitro-group into the nucleus has a similar effect (Forsyth and Pyman, *J.*, 1925, **127**, 573).

The triazoles listed in the Table were prepared by the fusion technique of which examples are given in the Experimental section.

Experimental

Light petroleum refers to the fraction of b. p. 60—80°, unless otherwise stated. A steady temperature could be maintained during the fusions by the use of the appropriate solvent in a three-neck flask; the centre neck contained a large (8″ × 1″) test tube and a reflux condenser was fitted to another neck.

Benzhydrazide Benzenesulphonate.—Benzhydrazide [104 g.; Curtius and Struve, *J. prakt. Chem.*, 1894, (2), **50**, 295], dissolved in the minimum amount of boiling alcohol (*ca.* 150 c.c.), was treated, in small portions and with shaking, with benzenesulphonic acid (140 g.; commercial). After the solution had been refluxed for 1 hr., a small amount of dry ether was added, and on cooling the product (84 g.; 37%) crystallized. *Benzhydrazide benzenesulphonate* crystallized from alcohol–ether as white needles, m. p. 169° (Found: C, 52·9; H, 4·9; N, 9·6. $C_{13}H_{14}O_4N_2S$ requires C, 53·1; H, 4·8; N, 9·5%).

Benzhydrazide toluene-p-*sulphonate* was prepared similarly from benzhydrazide and toluene-*p*-sulphonic acid monohydrate. It crystallized from alcohol–ether as white needles, m. p. 205° (Found: C, 51·1; H, 5·5; N, 8·6. $C_{14}H_{16}O_4N_2S,1H_2O$ requires C, 51·5; H, 5·5; N, 8·6%). The molecule of water was not lost even after several hours at 117°/0·5 mm.

p-*Nitrobenzhydrazide Benzenesulphonate.*—Benzenesulphonic acid (150 g.) was added, slowly and with shaking, to *p*-nitrobenzhydrazide [182 g.; Curtius and Trachmann, *J. prakt. Chem.*, 1895, (2), **51**, 168] dissolved in hot alcohol (4000 c.c.). The mixture was heated under reflux for 30 min. and cooled in an ice-bath; p-*nitrobenzhydrazide benzenesulphonate* (256 g.; 76%) crystallized from water as shiny, white plates, m. p. 254° (with frothing) (Found: C, 46·4; H, 4·0; N, 12·2; S, 9·5. $C_{13}H_{13}O_6N_3S$ requires C, 46·0; H, 3·9; N, 12·4; S, 9·5%).

α-*Picolinhydrazide Benzenesulphonate.*—Prepared as in the previous experiment, from α-picolinhydrazide (22·0 g.; Meyer and Mally, *Monatsh.*, 1912, **33**, 393), and benzenesulphonic acid (28·4 g.) in the minimum amount of boiling alcohol (200 c.c.), the *benzenesulphonate* crystallized from alcohol–ether (charcoal) as stout, golden needles, m. p. 150° (Found: C, 48·6; H, 4·5; N, 14·5. $C_{12}H_{13}O_4N_3S$ requires C, 48·8; H, 4·4; N, 14·3%).

3 : 5-*Diphenyl*-1 : 2 : 4-*triazole.*—(a) *New method.* A mixture of phenyl cyanide (3·0 g.; 0·029 mole) and benzhydrazide benzenesulphonate (9·4 g.; 0·032 mole) was heated at 200° for 3 hr. The cooled melt was extracted with cold sodium hydroxide solution (10%; *ca.* 500 c.c.); on acidification of this extract with concentrated hydrochloric acid a white precipitate (6·0 g., 92%; m. p. 169—170°) was obtained. 3 : 5-Diphenyl-1 : 2 : 4-triazole, after several crystallizations from dilute alcohol and then from light petroleum, was obtained as white needles, m. p. 190°. (b) *Pellazzari's method.* The product was isolated by extraction with alkali and precipitation with acid. It crystallized from methanol as white, opaque plates, and, after being dried at 117°/0·5 mm. for 3 hr., had m. p. 188—189°. The m. p. of a mixture with a specimen prepared by method (a) was 189°.

The acetyl derivative was prepared by use of acetic anhydride under reflux for 4 hr. (Atkinson and Polya, *loc. cit.*). It was prepared from the triazole prepared by each of the above methods, and separated from ether–light petroleum as rosettes of white needles, m. p. 107—108° (Pellizzari, *Gazzetta*, 1911, **41**, II, 20, gives m. p. 107—108°).

The picrate was prepared by use of an excess of picric acid in benzene. After 10 min. on the water-bath and cooling, and crystallization from benzene the derivative formed brilliant yellow plates, m. p. 166°, containing a molecule of benzene of crystallization. It lost benzene at 145° and began to decompose at 100°/0·5 mm. (Atkinson and Polya, *loc. cit.*, report m. p. 171°) (Found: C, 58·9; H, 3·7; N, 16·5. Calc. for $C_{20}H_{14}O_7N_6,C_6H_6$: C, 59·1; H, 3·8; N, 15·9%).

3-p-*Nitrophenyl*-5-*phenyl*-1 : 2 : 4-*triazole.*—Phenyl cyanide (5·0 g.; 0·048 mole) and *p*-nitrobenzhydrazide benzenesulphonate (17·9 g.; 0·053 mole) were heated at 200° for 3 hr.; slight frothing occurred and a small amount of a pale yellow substance, m. p. 170°, sublimed. After cooling, the crystalline melt was extracted with cold sodium hydroxide solution (10%; *ca.* 300 c.c.) and the extract acidified with concentrated hydrochloric acid. The precipitated 3-p-*nitrophenyl*-5-*phenyl*-1 : 2 : 4-*triazole* (11·2 g., 86%) was crystallized from methanol or acetone and then from light petroleum, forming white needles, m. p. 240° (Found: C, 63·2; H, 3·9; N, 20·6. $C_{14}H_{10}O_2N_4$ requires C, 63·1; H, 3·8; N, 21·0%).

5-*Phenyl*-3-α-*pyridyl*-1 : 2 : 4-*triazole.*—A mixture of phenyl cyanide (2·0 g.; 0·019 mole) and α-picolinhydrazide benzenesulphonate (6·3 g.; 0·021 mole) was heated at 200° for 3 hr. The reaction commenced with vigorous effervescence. The dark melt was extracted with sodium hydroxide solution (10%) and, on neutralization of the extract with concentrated hydrochloric acid, a pale pink solid (3·7 g., 86%) was precipitated. 5-*Phenyl*-3-α-*pyridyl*-1 : 2 : 4-

triazole crystallized from dilute alcohol as feathery, white needles, m. p. 212° (Found: C, 70·0; H, 4·7; N, 25·3. $C_{13}H_{10}N_4$ requires C, 70·3; H, 4·6; N, 25·1%).

The author is indebted to Dr. F. Lions under whose direction the early part of this work was carried out, and to Professor Sir Robert Robinson, O.M., F.R.S., for his interest. The spectra were measured by Mr. F. Hastings and Dr. F. B. Strauss.

THE UNIVERSITY OF SYDNEY, AUSTRALIA.
THE DYSON PERRINS LABORATORY, OXFORD.

[*Received, May 5th,* 1954.]

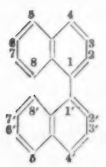
The Optical Resolution and Racemisation of Some Diisoquinolyls.

By MALCOLM CRAWFORD and I. F. B. SMYTH.

[Reprint Order No. 5377.]

Two new (5 : 5′- and 8 : 8′-) and a known (4 : 4′-) di*iso*quinolyl have been resolved optically. 1 : 1′-Di*iso*quinolyl (+)-tartrate mutarotates in solution. The active di*iso*quinolyls racemise rapidly in acid solution. Evidence is presented indicating that racemisation takes place by electrophilic hydrogen attack at one of the carbon atoms of the interannular bond, causing this atom to become tetrahedral. This mechanism is considered to operate generally during the racemisation of optically active diaryls.

FREE rotation about the interannular bond in 1 : 1′-dinaphthyl (I) is hindered, for although two of the four blocking positions (2 and 2′) remain filled with hydrogen atoms 1 : 1′-dinaphthyl-5 : 5′-dicarboxylic acid has been resolved into optical isomers (Bell and Morgan, *J.*, 1954, 1716). The mechanical obstruction to free rotation must be very slight. In one planar position it amounts only to the overlap of the van der Waals envelopes of the pairs of hydrogen atoms 2 : 8′ and 2′ : 8. The failure to resolve naphthidine [4 : 4′-diamino-derivative of (I)] (Bell and Morgan, *J.*, 1950, 1963), a finding now confirmed, is therefore not very surprising. Unexpectedly, however, the very similar compounds, 4 : 4′- and 5 : 5′-diquinolyl (I, with N in positions 4 : 4′ and 5 : 5′ respectively) were recently resolved by us (*J.*, 1952, 4133). Further resolutions of this type of compound have now been achieved with 1 : 1′-, 4 : 4′-, 5 : 5′-, and 8 : 8′-di*iso*quinolyl (I, with N in positions 2 : 2′, 3 : 3′, 6 : 6′ and 7 : 7′ respectively), with the reservation that active forms of the first were not isolated. Mutarotation of its (+)-tartrate occurred in solution. The half-lives of the active forms



(I)

TABLE 1.

Di*iso*quinolyl	Resolving acid	$[\alpha]_D$ maximum observed		Approx. half-life * Racemisation of base in N-HCl (min.)	Approx. half-life * Mutarotation of salt (min.)
1 : 1′	Tartaric	0°	0°	—	1·3 ± 0·3 (N-HCl)
4 : 4′	Tartaric	+1·65	−1·32	26 ± 11	5 ± 2 ($H{\cdot}CO{\cdot}NMe_2$)
5 : 5′	Tartaric	+0·97	−1·50	16 ± 5	20 ± 7 (EtOH)
8 : 8′	Malic	+0·69	−7·30	12 ± 1	—

* The limits for the half-life values have been computed on the basis of a ±0·02° error in polarimeter readings, which is generous.

of 4 : 4′- and 5 : 5′-diquinolyl in acid solution are 2·5 and 1·3 hr. respectively (Crawford and Smyth, *loc. cit.*). Table 1 shows that the active di*iso*quinolyls are much shorter-lived.

The di*iso*quinolyls resemble the parent substance, *iso*quinoline, in ultra-violet absorption (see Table 2) except that the bands are moved to slightly longer wave-lengths. This resemblance indicates that as in the diquinolyls there is a resistance to assumption of uniplanar form.

In 1 : 1′-di*iso*quinolyl (I, with N in positions 2 and 2′) there are no hydrogen atoms in the blocking positions 2 and 2′, but these are present during the attempted resolution as the substance is in the salt form. Even then there is a high rate of mutarotation. The same considerations apply to a smaller degree in the case of 8 : 8′-di*iso*quinolyl (I, with N

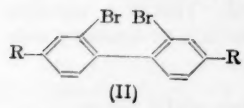
in positions 7 and 7'). The 7- and the 7'-hydrogen atom, present in the salt form, are absent in the free base. This absence of a substituent next to a blocking position may account for the rather high rate of racemisation even in acid solution in which a certain

TABLE 2. *Ultra-violet absorption of diisoquinolyls in ethanol.*

		Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.
1 : 1'	λ (mμ)	218	250	274	282	284	300	312	—	323·5
	ε	77,900	5660	7370	6800	6920	4450	6480	—	9430
4 : 4'	λ (mμ)	217	252	275	—	285	301	311	314	323·5
	ε	96,200	5760	8280	—	7800	5540	8120	7940	12,300
5 : 5'	λ (mμ)	217·3	249	276·5	279	285	303	310·5	316	323·5
	ε	96,200	6040	9290	9120	9600	6140	7350	6780	8880
8 : 8'	λ (mμ)	216·5	251	276	282·5	285	301	311	313	324
	ε	91,900	5220	8270	7830	7930	5030	7350	7280	11,400

concentration of free base will always be present. In 4 : 4'- and 5 : 5'-di*iso*quinolyl and diquinolyl the nitrogen atoms are not in blocking positions. These compounds are therefore comparable with the dinaphthyl derivatives already mentioned. Possible causes of optical stability and instability in such compounds will now be examined.

Interannular Conjugation.—The interannular bond in diphenyl has a length of 1·48 Å in the crystal, the two rings being coplanar (Dhar, *Indian J. Physics*, 1932, **7**, 43). The electron-diffraction method gives the value 1·54 Å for the vapour state (Karle and Brockway, *J. Amer. Chem. Soc.*, 1944, **66**, 1974), indicating non-coplanarity, which presumably obtains also in solution. In a dinaphthyl or diquinolyl the length of the interannular bond will likewise vary as the two halves of the molecule rotate. In either of the positions of coplanarity interannular conjugation will reach maximum and bond length minimum values. When substituents in non-blocking positions can assist this conjugation rotation might be correspondingly impeded by the bond shortening. Calvin (*J. Org. Chem.*, 1939, **4**, 256) has attempted to account for relative rates of racemisation of diphenyls along such lines. Recognising that amino-groups facilitate racemisation, *e.g.*, (II; R = NH_2) is unresolvable whereas (II; R = CO_2H) has a half-life of 5—10 min. at 0° (Searle and Adams, *J. Amer. Chem. Soc.*, 1934, **56**, 2112), he points out that in acid solution these groups are in the form NH_3^+ and therefore cannot participate in resonance and interannular bond shortening. This, however, does not account for the positive racemising effect of the introduction of the group. It is true that the heterocyclic nitrogen in 4 : 4'- and 5 : 5'-diquinolyl would be better able to conjugate with the interannular bond than in 4 : 4'- and 5 : 5'-di*iso*quinolyl, in agreement with the greater optical stability of the former, but this can be explained more satisfactorily by the electron-displacement hypothesis referred to below.

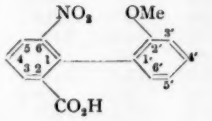
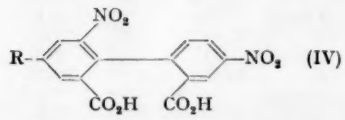


(II)

Buttressing Effect.—In 4 : 4'-di*iso*quinolyl (I, with N in positions 3 and 3') there are no hydrogen atoms attached in positions 3 and 3' next to the blocking positions. Any buttressing effect normally exerted by these hydrogens would be absent, thus permitting the hydrogens in the blocking positions to move apart more readily, so facilitating racemisation. Buttressing effects, however, are usually only observed in the case of large groups. Since 5 : 5'-di*iso*quinolyl, in which there can be little if any such effect, racemises more quickly than the 4 : 4'-isomer, this effect can be discounted.

Electron Displacement.—It is very significant that the resolvable compounds of the types being considered contain groups which are deactivating towards aromatic electrophilic substitution, namely, carboxyl or heterocyclic nitrogen of the pyridine type. When an activating group, namely, amino, is present resolution does not succeed. To be certain of such an effect a large number of compounds would have to be examined. Fortunately very extensive series of easily racemisable diphenyls containing three groups other than hydrogen in the blocking positions have been studied by Adams and others (for summaries, see Maitland, *Ann. Reports*, **1939**, **36**, 257; Gilman, "Organic Chemistry," 2nd Edn., Wiley, New York, **1943**, p. **362**; Remick, "Electronic Interpretations of Organic Chemistry," 2nd Edn., Wiley, New York, 1949, p. 296). In 2'-methoxy-6-nitrodiphenyl-2-carboxylic acid (III) substituted by various groups in positions 3', 4', or 5', Adams

measured the half-lives of the optically active isomers dissolved in acetone or ethanol. His relevant results are given in Table 3. No satisfactory, complete explanation has hitherto been given. The introduction of a substituent into the 3′-position in (III), *i.e.*, next to the blocking group, clearly retards racemisation either by a buttressing action or by forcing the methyl of the methoxyl group to swing round to the blocking side of the

(III)   (IV)

oxygen atom. The effect of groups in the 4′- or the 5′-position is more difficult to explain. Hanford and Adams (*J. Amer. Chem. Soc.*, 1935, **57**, 1592) noted a parallelism with dipole moment. Kuhn and Albrecht (*Annalen*, 1927, **458**, 221) attributed the slower racemisation of 4 : 6 : 4′-trinitrodiphenic acid (IV; R = NO_2) compared with 6 : 4′-dinitrodiphenic acid (IV; R = H) to an increased moment of inertia. In addition to other suggestions (Gilman, *op. cit.*) and that of Calvin (*loc. cit.*) Baddeley (*Nature*, 1946, **157**, 694) has discussed the effect of groups in increasing electron density in the ring containing them and the possibility of the 1′-carbon atom's becoming tetrahedral. This is a valuable suggestion and is closely related to the explanation advanced by us in a preliminary note (Crawford and Smyth, *Chem. and Ind.*, 1954, 346).

TABLE 3. *Half-lives (in minutes) of optically active derivatives of* (II) *(in the temperature range* 23—26° *in ethanol except where specified).*

	NO_2	Br	Cl	Me	OMe
3′	1905	827	711	331	98
4′	115 *	18	8	3·2	3·6 *
5′	35	32	31	11·5	10·8

No substituent: 9·4 minutes.

* In acetone, in which values were found to be of the same order as in ethanol (see Hanford and Adams, *loc. cit.*; Chien and Adams, *J. Amer. Chem. Soc.*, 1934, **56**, 1787; Yuan and Adams, *ibid.*, 1932, **54**, 4434; Stoughton and Adams, *ibid.*, p. 4426).

Table 3 lists the groups in the order in which Adams found them to confer optical stability, which is roughly the order of their size. The reverse order, OMe > Me > Cl > Br > NO_2, namely, that of their relative promotion of racemisation, is significantly also the order of their effectiveness in activating aromatic rings to electrophilic substitution. That they indeed act in this way is supported by relating their orientation and their influence on racemisation. The nitro-group, known to deactivate *ortho*- and *para*-substitution, retards racemisation more when in the 4′-position (*para*) than when in the 5′-position (*meta*), whereas all the others, especially methyl and methoxyl, which are highly activating to *ortho*- and *para*-substitution, cause speedier racemisation when in the 4′- than in the 5′-position. The conclusion can hardly be escaped that the racemisation is the result of electrophilic attack.

As discussed in the preliminary note such electrophilic attack by protium cation from the solvent will give rise to a transition state in which one of the carbon atoms of the interannular bond becomes tetrahedral so facilitating rotation about this bond.

Among 1 : 1′-dinaphthyls the non-resolvability of naphthidine is now seen to be due to the two amino-groups, which are suitably placed to activate the 1- and the 1′-position to electrophilic attack. The optical stability of 1 : 1′-dinaphthyl-5 : 5′-dicarboxylic acid on the other hand is due to the deactivating effect of the two carboxyl groups. The same considerations account for the resolvability of (II; R = CO_2H) in contrast to the non-resolvable (II; R = NH_2). Similarly in 4 : 4′- and 5 : 5′-diquinolyl the strong deactivating effect of heterocylic nitrogen of the pyridine type is felt in the 4 : 4′- and the 5 : 5′-positions respectively, thus accounting for the unexpected resolvability of these compounds. In 4 : 4′- and 5 : 5′-di*iso*quinolyl, however, the heterocyclic nitrogen atom cannot conjugate directly with the interannular bond and so the deactivation is much reduced. This is

reflected in the faster racemisation of the latter compounds. The greater optical stability of (IV; R = NO_2) than of (IV; R = H) is also adequately explained by the presence of an additional deactivating nitro-group in the *para*-position to the interannular bond.

It is doubtful whether racemisation of hindered diaryls by a mutual slipping-past of the interfering groups plays as important a rôle as believed. The fact that the diquinolyls and other related compounds can be obtained in optically active forms indicates that the overlap of van der Waals envelopes must offer appreciable resistance to slip-past. Overlap of atoms, as distinct from van der Waals envelopes, as in the case of most resolvable diaryls must constitute an almost insuperable barrier to slip-past. In such a process, bending of bonds or interpenetration of atoms or both is involved. For either of these to occur to any extent would require considerable activation energy, certainly much more than racemisation by conversion of the carbon atoms concerned into tetrahedral forms.

Racemisation of the type postulated represents a bimolecular reaction whereas passage through a uniplanar transition state must be unimolecular. The first-order kinetics found by Kuhn and Albrecht (*loc. cit.*; *Annalen*, 1927, **455**, 272) for the recemisation of some substituted diphenic acids would, however, be expected in either case, for their measurements were carried out in aqueous solution. Participation of solvent in the electrophilic attack would result in a *pseudo*-first-order reaction.

Experimental

Absorption Spectra.—These were determined with a Unicam SP500 Spectrophotometer.

Attempted Resolution of 1 : 1′-*Diisoquinolyl.*—(+)-Tartaric acid (0·375 g.) was added to a solution of 1 : 1′-di*iso*quinolyl (0·512 g.) in hot ethanol (3·0 ml.); the base was prepared according to Case (*J. Org. Chem.*, 1952, **17**, 471). After all had dissolved the cooled solution deposited a basic *tartrate* (0·31 g.), m. p. 164—165°, containing three mols. of base to one of acid (Found: C, 76·1; H, 4·7; N, 9·1. $C_{58}H_{42}O_6N_6$ requires C, 75·7; H, 4·6; N, 9·1%). Treatment of the filtrate with cold ammonia solution precipitated the base (0·21 g.), whose solution in N-hydrochloric acid, examined 5 min. later, was optically inactive.

Mutarotation of 1 : 1′-*Diisoquinolyl Basic Tartrate.*—A filtered solution of the basic tartrate (0·3 g. in 2·5 ml. of N-HCl) gave the following polarimeter readings in a 1-dm. tube: 5 min. after dissolution, α_D^{24} −0·30°; 5½ min. −0·22°; 6½ min. −0·09; 8½ min. −0·02°; 12½ min. +0·03°; 65 min. +0·05°; several hours +0·07°.

Resolution of 4 : 4′-*Diisoquinolyl.*—To (+)-tartaric acid (3 g. in 20 ml. of hot ethanol) was added 4 : 4′-di*iso*quinolyl, m. p. 149—150° (2·56 g. in 20 ml. of hot ethanol) (Ueda, *J. Pharm. Soc. Japan*, 1940, **60**, 536, through *Chem. Abs.*, 1941, **35**, 1791; *J. Pharm. Soc. Japan*, 1940, **60**, 210, through *Chem. Zentr.*, 1941, II, 480, and *Brit. Abs.*, 1941, *A* II, 337). After filtration and cooling, a *hydrogen tartrate* (2·64 g.) separated, having m. p. 197° (decomp.) (Found: C, 64·5; H, 4·3; N, 6·9. $C_{26}H_{22}O_{12}N_2$ requires C, 65·0; H, 4·5; N, 6·9%). In dimethylformamide solution (1 g. in 15 ml.) the following polarimeter readings were obtained in a 2-dm. tube: 3 min. after dissolution, α_D^{25} +0·03°; 8 min. +0·10°; 13 min. +0·14°; 73 min. +0·17° (final value). A portion (1·5 g.), suspended in ethanol, was decomposed with cold ammonia solution, thus liberating the active *base* (0·96 g.) (Found: C, 83·6; H, 4·8; N, 10·9. $C_{18}H_{12}N_2$ requires C, 84·4; H, 4·7; N, 10·9%). Its solution (0·90 g. in 17 ml. of N-HCl) in a 2-dm. polarimeter tube gave the following readings: 15 min. after dissolution, α_D^{25} −0·14°; 75 min. −0·03°; 120 min. 0°.

The mother-liquor from which the tartrate had crystallised was decomposed at once with cold ammonia solution, giving the active *base* (0·50 g.), m. p. 149°. Its solution (0·5 g. in 15 ml. N-HCl) in a 2-dm. tube gave the following readings: 8 min. after dissolution α_D^{25} +0·11°; 68 min. +0·01°; 128 min. 0°.

5 : 5′-*Diisoquinolyl.*—To a refluxing mixture of 5-bromo*iso*quinoline (10 g.), 1% palladium–calcium carbonate (10 g.), and 5% methanolic potassium hydroxide (500 ml.), there was added 90% hydrazine hydrate (10 ml.) slowly during 30 min. with stirring. A similar amount of hydrazine hydrate was added after another 30 min. The stirring and refluxing was continued for 8 hr. The hot liquid was then filtered, the residue was washed with boiling methanol, and the filtrate and washings were evaporated to small bulk with additions of water. A dark oil separated which solidified on cooling. This solid, dissolved in dilute hydrochloric acid (100 ml.), was decolorised by shaking with carbon for an hour and then reprecipitated with ammonia solution. Two recrystallisations from benzene–ligroin gave 5 : 5′-*diisoquinolyl* (2·2 g.) as colourless prisms, m. p. 159—160° (Found: C, 84·3; H, 4·9; N, 10·7%).

Resolution of 5 : 5′-*Diisoquinolyl.*—Solutions of 5 : 5′-di*iso*quinolyl (2·56 g.) and (+)-tartaric acid (3 g.) in hot ethanol (total vol. 50 ml.) were mixed, filtered hot, and cooled to 5°. A tartrate (3·42 g.) crystallised. This became gummy at room temperature, probably owing to loss of alcohol of crystallisation. It also separated from solution as a gum at room temperature. A portion was dried at room temperature and decomposed with cold ammonia solution. The active base (1 g. in 15 ml. of N-HCl) in a 2-dm. tube gave the following readings: 6 min. after dissolution α_D^{24} −0·20°; 21 min. −0·09°; 51 min. −0·03°; overnight 0°.

A portion of the mother-liquor left after the separation of the tartrate gave the following readings in a 2-dm. tube: α_D^{24} +0·79° ($[\alpha]_D^{24}$ +9·23°), after 15 min. +0·74°; 45 min. +0·67°; 75 min. +0·64° (final value). The remainder was decomposed to the active base (0·75 g.), a solution of which (0·7 g. in 15 ml. of N-HCl) gave the following readings in a 2-dm. tube: 6 min. after dissolution α_D^{24} +0·09°; 36 min. +0·02°; 66 min. +0·01°.

8 : 8′-*Diisoquinolyl.*—Reduction of 8-bromo*iso*quinoline (3·87 g.) with hydrazine hydrate similarly to the 5-isomer gave 8 : 8′-*diisoquinolyl* (0·51 g.) as prisms (from benzene–ligroin or leaflets from ethanol), m. p. 153—154° (Found: C, 83·9; H, 4·8; N, 10·9%).

Resolution of 8 : 8′-*Diisoquinolyl.*—Solutions of 8 : 8′-di*iso*quinolyl (0·64 g.) and (−)-malic acid (0·67 g.) in hot ethanol (total vol. 10 ml.) were mixed, filtered, and cooled. A *malate* separated (0·50 g.), having m. p. 145° (Found: C, 66·7; H, 5·1; N, 6·9. $C_{22}H_{18}O_5N_2$ requires C, 67·7; H, 4·7; N, 7·2%). A portion (0·3 g.) was decomposed with cold ammonia solution, to give the active base (0·12 g.), which (2·5 ml. in N-HCl) gave the following readings in a 1-dm. tube: 5 min. after dissolution, α_D^{23} −0·35°; 25 min. −0·09°; 40 min. −0·06°; overnight, 0°.

The mother-liquor after separation of the malate was decomposed with cold ammonia solution, so freeing the active base of opposite sign (0·23 g.), m. p. 154°. Its solution (0·18 g. in 2·5 ml. of N-HCl) in a 1-dm. tube gave the following readings: 6 min. after dissolution, α_D^{23} +0·05°; 30 min. +0·02°; overnight, 0°.

Attempts to Resolve Naphthidine.—Naphthidine camphorsulphonate was prepared separately in ethanol, ethanolic chlorobenzene, and aqueous dimethylformamide. The tartrate was also prepared in ethanolic chlorobenzene. In no case was mutarotation observed in solutions of these salts nor was active base obtained.

COLLEGE OF TECHNOLOGY, BELFAST. [*Received, May 10th,* 1954.]

Infra-red Spectra of Carbohydrates. Part II. Anomeric Configuration of Some Hexo- and Pento-pyranoses.*

By S. A. BARKER, E. J. BOURNE, R. STEPHENS, and D. H. WHIFFEN.

[Reprint Order No. 5385.]

In Part I, the infra-red spectra (730—960 cm.$^{-1}$) of D-glucopyranose and of its *O*-methyl derivatives were discussed, and systematic differences between the α- and the β-series were observed. In this paper, similar consideration is given to the acetates of D-glucopyranose, and to derivatives of galactopyranose, mannopyranose, xylopyranose, and arabopyranose. The new spectra provide additional evidence for the tentative assignments given in Part I, and are in agreement with the rules governing the assumption by a sugar of its more stable chair form.

IN previous communications (Barker, Bourne, Stacey, and Whiffen, *Chem. and Ind.*, 1953, 196; Part I *) it was shown that the infra-red spectra of D-glucopyranose derivatives display, in the frequency range 730—960 cm.$^{-1}$, three principal sets of bands. Type 1, exhibited by α-anomers at 917 ± 13 cm.$^{-1}$, and by β-anomers at 920 ± 5 cm.$^{-1}$, was attributed tentatively to a ring vibration analogous to that shown by tetrahydropyran at 875 cm.$^{-1}$ (cf. Burket and Badger, *J. Amer. Chem. Soc.*, 1950, **72**, 4397), which includes a considerable contribution from the ring C–O–C antisymmetrical stretching. Type 2, revealed by α-anomers at 844 ± 8 cm.$^{-1}$, and by β-anomers at 891 ± 7 cm.$^{-1}$, was believed to be one of the $C_{(1)}$–H deformation modes. Type 3, shown by α-anomers at 766 ± 10 cm.$^{-1}$,

* Part I, *J.*, 1954, 171.

and by β-anomers at 774 ± 9 cm.$^{-1}$, was suspected of being the ring breathing frequency exhibited by tetrahydropyran at 813 cm.$^{-1}$ (Burket and Badger, *loc. cit.*).

The present investigation was instigated to determine whether vibrations of types 1, 2, and 3 were exhibited by acetates of D-glucopyranose, and by derivatives of the pyranose forms of other hexoses and of pentoses. It was also an attempt to obtain further evidence for the tentative assignments given to these vibrations in Part I.

Experimental

The spectra were measured with a Grubb–Parsons single-beam spectrometer, with a sodium chloride prism, by the " Nujol " mull technique. The derivatives investigated were crystalline, unless otherwise stated, and wherever possible their authenticity was confirmed by melting point and specific rotation. The Tables show the frequencies (cm.$^{-1}$) of the absorption bands, together with indications of their relative intensities. They list also those carbon atoms in the pyranose rings which carry an equatorial hydrogen atom; the assumptions made in determining these carbon atoms are (i) that a pyranose ring takes up a chair form in preference to any boat form whenever both are structurally possible, and (ii) any axial substituent (other than hydrogen) on the pyranose ring introduces an element of instability into the conformation—especially important are an axial oxygen atom on position 2 when its C–O valency bisects the two C–O valencies of carbon atom 1, and an axial hydroxymethyl group at position 5 on the same side of the ring as an axial hydroxyl, or substituted hydroxyl, group (Reeves, *J. Amer. Chem. Soc.*, 1950, **72**, 1499).

Discussion

Identification of Anomers.—The use of the type 2 absorption peaks in the determination of anomeric configuration (Part I) has been extended to other monosaccharide derivatives of D-glucose, particularly those containing the *O*-acetyl group (Table 1). All those having the α-configuration displayed type 2*a* absorption at 843 ± 4 cm.$^{-1}$. This region was transparent in the spectra of those β-anomers given in Table 1. However, derivatives of β-D-glucose in which a benzene ring was incorporated (*e.g.*, phthalimido- and trityl derivatives) sometimes displayed absorption in this region due to the benzene ring (*e.g.*, methyl 2 : 3 : 4-tri-*O*-acetyl-6-deoxy-6-phthalimido-β-D-glucopyranoside, 836 m; phenyl α-D-glucopyranoside, 836 s; phenyl β-D-glucopyranoside, 827 m).

Type 2*a* absorption is shown also by octa-acetates of disaccharides in the D-glucose series possessing at least one of the sugar moieties in the α-configuration, irrespective of whether this α-unit constitutes the non-reducing (*e.g.*, β-*iso*maltose octa-acetate, 825 cm.$^{-1}$; β-maltose octa-acetate, 834 cm.$^{-1}$) or the reducing (*e.g.*, α-cellobiose octa-acetate, 840 cm.$^{-1}$; α-gentiobiose octa-acetate, 840 cm.$^{-1}$) portion of the disaccharide.

All the acetates of β-D-glucopyranose examined gave an absorption band (type 2*b*), of moderate or strong intensity, at 890 ± 8 cm.$^{-1}$ (Table 1). As stated in Part I, some of the type 1 absorptions of the α-compounds lie in the same range as the type 2*b* absorptions of the β-compounds, and so the presence of a band at *ca.* 890 cm.$^{-1}$ is not conclusive evidence for a β-glucose unit. There is an additional complication when dealing with acetates inasmuch as the ester groups themselves absorb near this frequency region.

An examination of the infra-red spectra of *O*-methyl- and *O*-acetyl-pyranose derivatives of other aldohexoses and of aldopentoses, of their methyl-glycosides, and of the free sugars themselves, revealed the results given in Tables 2, 3, and 4; the mean frequencies and standard deviations for the hexoses are summarised in Table 5.

It will be seen that the pyranose derivatives of mannose and galactose resemble those of glucose in that they display absorption bands of types 2(*a* or *b*) and 3, and probably also of type 1, but the high proportion of acetates in the compounds available made it impossible to distinguish bands of the latter type from other C–O–C vibrations. The type 2*a* absorption, which is so useful for characterising derivatives of α-D-glucose, was shown by all the α-galactose and α-mannose compounds, but unfortunately a few of the β-anomers showed a band in the same region; further work will be necessary before it can be decided whether these apparent anomalies were in fact due to impurities. In the

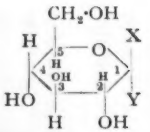


TABLE 1. *Derivatives of* D-*glucopyranose.*

α-D-Glucopyranose: X = H; Y = OH. Equatorial hydrogen on $C_{(1)}$.
β-D-Glucopyranose: X = OH; Y = H. No equatorial hydrogen atoms.
The conformation in each case above is C1 (Reeves, *loc. cit.*).
Key: br = broad; m = moderate strength; s = strong; v = very; w = weak.

Compound	Frequencies (cm.$^{-1}$) of absorption peaks: C–O–C vibrations, type 1, etc.					Type 2*b*?	Other peaks	Type 2*a*	Type 3
α-D-Glucopyranose	—	—	914 s	—	—	—	—	837 s	774 s
1 : 3 : 4 : 6-tetra-*O*-acetyl-2-deoxy-	956 s	927 vs	911 s	902 s	876 w	—	865 vw †	849 m	747 m
2-acetamido-1 : 3 : 4 : 6-tetra-*O*-acetyl-2-deoxy-	942 s	—	914 w	896 w	884 w	—	—	842 w	745 w
1 : 2 : 3 : 4-tetra-*O*-acetyl-6-*O*-methyl-	942 m	926 s	916 s	898 s	891 s	—	—	847 w	741 m
1 : 2 : 3 : 4 : 6-penta-*O*-acetyl-	942 vs	935 vs	911 s	905 s	886 m	—	—	841 s	743 m
2 : 3 : 4 : 6-tetra-*O*-acetyl-1-bromo-1-deoxy-	—	925 vs	910 s	892 m	—	—	—	845 s	751 m
Methyl α-D-glucopyranoside	—	—	—	896 s	—	—	—	840 s	745 s
3 : 4 : 6-tri-*O*-acetyl-2-*O*-methyl-	—	922 vs	—	—	888 s	—	—	842 w	754 s, 743 s
β-D-Glucopyranose	—	—	909 m	—	—	896 vs	856 w *	—	—
1 : 2 : 3 : 4-tetra-*O*-acetyl-	956 m	927 m	909 s	—	882 m	897 m	—	—	781 w
1 : 2 : 3 : 4 : 6-penta-*O*-acetyl-	949 m	938 m	911 m	—	872 w	898 m	—	—	—
Methyl β-D-glucopyranoside	961 s	—	—	—	—	884 s	—	—	783 m
2 : 3 : 4-tri-*O*-acetyl-	966 m	935 vw	907 s	—	—	876 m	—	—	—
2 : 3 : 4-tri-*O*-acetyl-6-bromo-6-deoxy-	957 m	—	903 vs	—	—	885 m	853 w *	—	—
2 : 3 : 4 : 6-tetra-*O*-acetyl-	949 m	—	911 s	903 vs	867 m	894 vs	—	—	—
3-acetamido-2 : 4 : 6-tri-*O*-acetyl-3-deoxy-	—	924 m	908 m	—	—	892 s	828 w	—	731 m

* Possibly due to a trace of the α-anomer. † Probably due to the CH_3-group.

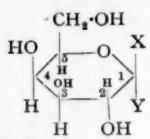


TABLE 2. *Derivatives of* D-*galactopyranose.*

α-D-Galactopyranose: X = H; Y = OH. Equatorial hydrogens on $C_{(1)}$ and $C_{(4)}$.
β-D-Galactopyranose: X = OH; Y = H. Equatorial hydrogen on $C_{(4)}$.
The conformation in each case above is C1 (Reeves, *loc. cit.*).

Compound	Frequencies (cm.$^{-1}$) of absorption peaks: C–O–C vibrations, type 1, etc.				Type 2*b*	Type 2*c*	Other peaks	Type 2*a*	Other peaks	Type 3
α-D-Galactopyranose	953 vs	—	—	—	—	888 vw	—	833 vs	792 vs	764 vs
1 : 2 : 3 : 4-tetra-*O*-acetyl-6-deoxy-	947 m	926 vs	898 s	—	—	868 w	—	820 m	—	737 s
2 : 3 : 4 : 6-tetra-*O*-acetyl-1-bromo-1-deoxy-	942 s	907 vs	894 s	884 s	—	870 m	857 m	839 m	822 w	757 m, 743 m
Methyl α-D-galactopyranoside	—	923 s	—	—	—	868 s	—	818 vs	—	784 vs
2 : 3 : 4 : 6-tetra-*O*-acetyl-	947 s	936 vs	907 vs	890 s	—	868 w	846 w	833 m	820 w	757 s, 748 s
6-deoxy-2 : 3 : 4-tri-*O*-methyl-	947 vs	—	907 s	—	—	859 m	—	810 vs	—	736 vs
β-D-Galactopyranose	943 m	—	—	—	897 s	881 s	—	—	831 mbr *	776 vs
1 : 2 : 3 : 4 : 6-penta-*O*-acetyl-	956 s	928 m	914 m	—	896 vs	865 s	—	—	—	725 m
6-deoxy-	961 s	—	—	—	914 m	876 m	—	—	814 vs	768 m
Methyl β-D-galactopyranoside	—	940 m	—	—	887 m	868 s	—	—	821 vw	782 s
2 : 3 : 4-tri-*O*-methyl-	—	933 m	—	—	888 m	870 m	—	—	—	757 vs
6-deoxy-2 : 3 : 4-tri-*O*-methyl-	958 s	935 m	—	—	886 s	872 s	—	—	—	727 s
2 : 3 : 4 : 6-tetra-*O*-methyl-	—	933 m	—	—	898 s	872 m	—	—	—	751 vs
2 : 3 : 4 : 6-tetra-*O*-acetyl-	952 vs	—	905 vs	—	896 s	879 w, 868 s	—	—	—	727 s

* Possibly due to the α-anomer.

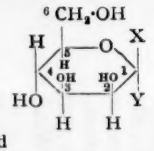


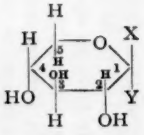
TABLE 3. *Derivatives of mannopyranose.*

α-D-Mannopyranose: X = H; Y = OH. Equatorial hydrogens on $C_{(1)}$ and $C_{(2)}$.
β-D-Mannopyranose: X = OH; Y = H. Equatorial hydrogen on $C_{(2)}$.
The conformation in each case above is C1 (Reeves, *loc. cit.*).

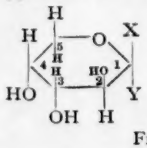
Compound	Frequencies (cm.$^{-1}$) of absorption peaks: C–O–C vibrations, type 1, etc.				Type 2*b*	Type 2*c*	Other peaks	Type 2*a*	Type 3	Other peaks
α-D-Mannopyranose										
3 : 4-di-*O*-methyl-, monohydrate ...	966 m	937 w	913 w	—	—	878 m	—	841 s	794 vs	746 s
3 : 4 : 6-tri-*O*-methyl-	966 vs	947 vs	—	894 s	—	871 s	—	818 s	791 vs	—
α-L-Mannopyranose										
6-deoxy-, monohydrate	973 vs	—	907 s	—	—	872 s	—	824 s	798 vs	—
Methyl α-D-mannopyranoside	972 s	—	914 w	—	—	888 w	—	843 m	808 s	—
2 : 3 : 4-tri-*O*-acetyl-	965 vs	928 vs	916 vs	—	—	886 vs	—	837 w	818 m, 789 s	756 vs
2 : 3 : 4 : 6-tetra-*O*-acetyl-	—	935 s	911 m	900 m	—	886 w	—	830 w	792 m	—
2 : 3 : 4 : 6-tetra-*O*-methyl-	966 vs	951 vs	925 m	901 w	—	876 s	—	840 s	792 s	—
Methyl α-L-mannopyranoside										
6-deoxy-	961 vs	—	905 s	—	—	874 s	—	833 s	799 s	—
2 : 3 : 4-tri-*O*-acetyl-6-deoxy-	974 vs	949 vs, 935 vs	905 vs	898 vs	—	881 vs	—	834 s	795 s, 788 s	—
β-D-Mannopyranose	—	938 m	—	—	896 m	861 m	854 m	—	770 s	—
1 : 2 : 3 : 4 : 6-penta-*O*-acetyl-	971 s	947 vs, 933 vs	905 s	—	888 s	880 s	850 w	—	756 s	—
Mannan (1 : 4-β-polysaccharide)	—	938 s	—	—	888 m	867 s	—	—	812 s, 803 vs	—
Methyl β-D-mannopyranoside *	—	947 m	928 m	—	896 m	875 m	830 m	—	795 s	—
2 : 3 : 4 : 6-tetra-*O*-acetyl-	956 vs	947 vs	—	—	898 vs	863 s	—	—	747 s	—

* Syrup.

TABLE 4. *Derivatives of xylopyranose and arabopyranose.*



α-D-Xylopyranose: X = H; Y = OH. Equatorial hydrogen on $C_{(1)}$.
β-D-Xylopyranose: X = OH; Y = H. No equatorial hydrogen atoms.
The conformation in each case above is C1 (Reeves, *loc. cit.*).



α-D-Arabopyranose: X = H; Y = OH. Equatorial hydrogen on $C_{(4)}$.
β-D-Arabopyranose: X = OH; Y = H. Equatorial hydrogens on $C_{(1)}$ and $C_{(4)}$.
The conformation in each case above is 1C (Reeves, *loc. cit.*).

Compound	Frequencies (cm.$^{-1}$) of absorption peaks	830—855 cm.$^{-1}$	Type 3
α-D-Xylopyranose	933 s, 903 s	—	760 s
2 : 3 : 4-tri-*O*-methyl-	935 vs, 903 vs, 892 vs	—	742 s
2 : 3 : 4-tri-*O*-acetyl-	929 s, 914 s, 898 m, 889 m, 878 s	—	759 s
2 : 3 : 4-tri-*O*-acetyl-1-bromo-1-deoxy-	934 vs, 901 vs, 882 s, 873 vs	—	753 m, 740 s
Methyl α-D-xylopyranoside	938 s, 896 s	—	740 s
β-L-Xylopyranose			
1 : 2 : 3 : 4-tetra-*O*-acetyl-	940 m, 909 s, 895 s, 878 s	—	—
Xylan (β-1 : 4-D-polysacc.)	895 m	—	—
2 : 3-di-*O*-acetyl-	930 w, 894 s, 876 s	—	—
Methyl β-D-xylopyranoside	935 m, 920 m, 896 s	—	—
2 : 3 : 4-tri-*O*-methyl-	937 m, 886 s	—	—
α-D-Arabopyranose			
1 : 2 : 3 : 4-tetra-*O*-acetyl-	947 m, 914 m, 898 m, 879 w, 861 w	—	749 s
Methyl α-D-arabopyranoside	938 vs, 914 s, 878 s	—	776 s, 772 s
β-D-Arabopyranose	941 m, 890 s	840 s	781 vs
2 : 3 : 4-tri-*O*-acetyl-1-bromo-1-deoxy- (L-isomer)	938 s, 930 s, 890 s, 870 m	853 s	759 s
Methyl β-D-arabopyranoside	944 m, 923 m, 882 s	843 m, 836 m	775 s
2 : 3 : 4-tri-*O*-methyl-	933 vs, 905 s	854 s	744 vs

arabinose series, the presence or absence of absorption at 830—855 cm.$^{-1}$ again seems to afford a good method of differentiating between α- and β-forms; it is interesting that in this case it is the β-compounds which show the absorption in the region of the 2*a* band of hexoses, but we prefer at this stage not to assign the vibration. The xylopyranose series

TABLE 5.

Pyranose sugar derivatives of :	Absorption (cm.$^{-1}$) of : Type 2*a*	Type 2*b*	Type 2*c*	Type 3
α-D-Glucose	843 ± 4	—	—	753 ± 17
β-D-Glucose	—	890 ± 8		
α-D-Galactose	825 ± 11	—	871 ± 7	752 ± 20
β-D-Galactose	—	895 ± 9		
α-D-Mannose	833 ± 8	—	876 ± 9	791 ± 18
β-D-Mannose	—	893 ± 6		

is exceptional inasmuch as neither the α- nor the β-anomers show absorption at 830—855 cm.$^{-1}$; however, the presence or absence of type 3 absorption (749 ± 10 cm.$^{-1}$) can apparently be used here for the differentiation of anomers.

It is to be expected that optical enantiomorphs will show identical infra-red spectra (provided that they have been isolated in the same crystalline form), and this was found to be the case, over the frequency range 1790—630 cm.$^{-1}$, for the D- and L-forms of β-arabopyranose, methyl α-arabopyranoside, β-xylopyranose tetra-acetate, and α-xylopyranose. It follows, therefore, that the conclusions reached above are equally valid for the D- and the L-series.

Type 2*c* absorption, displayed by derivatives of D-galactopyranose and D-mannopyranose (irrespective of their anomeric configuration) but not by derivatives of D-glucose, seems to offer a useful method for distinguishing between derivatives of these three hexoses which are identically substituted. In addition it may prove valuable in the polysaccharide field for distinguishing a polyglucosan from a polymannan or a polygalactan. It is shown also by the galactose-containing disaccharides; for example, melibiose and lactose each has a peak at 872 cm.$^{-1}$, which is absent from the spectra of *iso*maltose and cellobiose.

Caution must be exercised in any interpretation of the infra-red spectra of syrups since a marked peak movement was observed in passing from crystalline to syrupy glucose. A syrupy α,β-mixture of D-glucose showed both type 2*a* and 2*b* absorption peaks, but these were somewhat displaced from their usual positions. Thus absorption of type 2*a*, present in crystalline α-D-glucose at 837 cm.$^{-1}$, now appeared at 849 cm.$^{-1}$.

Evidence for Assignment.—It was suggested in Part I that the vibrations associated with type 2*a* and 2*b* absorptions were C–H deformations in which the hydrogen on $C_{(1)}$ was involved intimately. It was believed that the difference between the α- and the β-glucose frequencies was related to the fact that this hydrogen atom in the α-anomer lies in the equatorial belt of the chair form of the six-membered ring and in the β-anomer in the axial position. It may be that, as in tetrahydropyran (Burket and Badger, *loc. cit.*), the axial hydrogen atoms on $C_{(1)}$ and $C_{(5)}$ of a pyranose sugar ring are closer together than in *cyclo*hexane, and those on $C_{(2)}$ and $C_{(4)}$ are further apart. Since the most stable conformation of a D-glucopyranose ring involves an axial hydrogen atom on $C_{(5)}$, it is possible that during deformation the axial hydrogen atoms on $C_{(1)}$ and $C_{(5)}$ come into van der Waals contact, or very nearly so, and that this leads to an increased frequency.

Additional evidence for the assignment of type 2*a* absorption to an equatorial $C_{(1)}$–H deformation is that, besides derivatives of α-D-glucopyranose, those of α-D-galactopyranose and α-D-mannopyranose also display type 2*a* absorption (Table 5), and this absorption is independent of *O*-substituents. All of these sugars, in the most stable conformation of their pyranose rings, are known to have an equatorial hydrogen atom on $C_{(1)}$. It remains to be seen whether pentoses in general exhibit type 2*a* absorption; if they do, then the absorption at 830—855 cm.$^{-1}$ in derivatives of β-D-arabinose is consistent with this generalisation, and the only exceptions, as yet, are the derivatives of α-D-xylopyranose which have a $C_{(1)}$–H in the equatorial position and yet fail to display absorption in this

range. The reason for this may be that the lack of a hydroxymethyl group on $C_{(5)}$ and the absence of any axial hydroxyl group round the ring (other than on $C_{(1)}$) markedly reduce the change of dipole moment during the equatorial $C_{(1)}$–H deformation.

Type 2*b* absorption is shown by derivatives of β-D-glucopyranose, β-D-galactopyranose, and β-D-mannopyranose, all of which have an axial $C_{(1)}$–H in their most stable conformation. If this generalisation is applicable to pentoses, then suitable candidates can be found in the spectra of pyranose derivatives of α-D-arabinose and β-D-xylose.

In a strict comparison of the corresponding derivatives of D-galactopyranose and D-mannopyranose with those of D-glucopyranose, the derivatives of the two former hexoses almost invariably displayed an extra absorption peak (type 2*c*) at *ca.* 875 cm.$^{-1}$ (Table 5), which appeared to be independent of *O*-substituents, and of anomeric character. It is believed that this absorption is due to deformations of the equatorial C–H bonds at positions 4 and 2 in galactopyranose and mannopyranose, respectively. Such a rise of frequency from *ca.* 840 cm.$^{-1}$ for a $C_{(1)}$–H equatorial deformation to *ca.* 875 cm.$^{-1}$ for a $C_{(2)}$–H or $C_{(4)}$–H equatorial deformation is consistent with subjection of the equatorial hydrogen atoms on $C_{(2)}$ and $C_{(4)}$ to van der Waals forces from neighbouring groups which are stronger than those affecting the equatorial hydrogen on $C_{(1)}$.

Finally, to the question of the value of the deformation frequency of an axial C–H group, other than $C_{(1)}$–H, no answer can be given because the region above 890 cm.$^{-1}$, where such an absorption might occur, also contains absorption peaks due to type 1 vibrations and to the in-phase C–O stretching mode of methyl ethers and of acetates.

As mentioned in Part I, the type 3 peak intensity is very sensitive to changes in sugar configuration; thus decreased intensity was observed in derivatives of β-D-glucopyranose, which possesses no axial C–O bonds. This decrease is even more marked in derivatives of β-D-xylopyranose, which differs from β-D-glucopyranose only in the absence of a hydroxymethyl group on $C_{(5)}$, no absorption of type 3 being observed in any derivative so far studied. The symmetrical character of the vibration is emphasised also by *scyllo*inositol, a centrosymmetrical cyclitol, in which all the C–O bonds are equatorial, and which does not display type 3 absorption in the infra-red, in agreement with the selection rules. The lower frequencies of the type 3 absorption in sugars, and more particularly of their fully substituted acetates, compared with that observed in tetrahydropyran (813 cm.$^{-1}$), is to be expected from the extra weight involved.

Since the publication of our first paper on this topic, Whistler and House (*Analyt. Chem.*, 1953, **25**, 1463) have reported independently that infra-red spectra can be used to distinguish between anomeric forms of carbohydrates; many of the characteristic bands were however in a higher frequency range than those reported herein.

The authors are indebted to Professor M. Stacey, F.R.S., for his close interest in this work and for providing reference compounds from his collection. They are also indebted to many other colleagues for the generous provision of samples. They thank the British Rayon Research Association and Courtaulds' Scientific and Educational Trust Fund for the award of scholarships (to S. A. B. and R. S.), and the Royal Society for a grant for the purchase of the spectrometer. A contribution to the expenses of the investigation was made by the British Rayon Research Association.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

[*Received, May 14th*, 1954.]

Alkyl–Oxygen Fission in Carboxylic Esters. Part XIV. 4-Methyldiphenylmethyl and 2 : 4 : 6-Trimethyldiphenylmethyl Compounds.*

By A. G. Davies, J. Kenyon, B. J. Lyons, and T. A. Rohan.

[Reprint Order No. 5391.]

4-Methyldiphenylmethanol and 2 : 4 : 6-trimethyldiphenylmethanol have been resolved by fractional crystallisation of the alkaloidal salts of their hydrogen phthalic esters. These alcohols and their esters, by virtue of inductive and hyperconjugative electron release from the methyl groups, undergo unimolecular alkyl–oxygen fission reactions more readily than the corresponding diphenylmethyl compounds, but less readily that the analogous methoxy-substituted compounds.

Earlier papers in this series have demonstrated that the introduction of α-aryl groups into the alkyl group of alcohols and their carboxylic esters greatly increases the tendency of these compounds to react by a unimolecular alkyl–oxygen fission mechanism. This is particularly marked when the aryl group carries *ortho*- and/or *para*-electron-releasing substituents, such as alkoxy-groups (Part XII, *J.*, 1953, 3619), alkylthio-groups (Part VIII, *J.*, 1951, 382), or dialkylamino-groups (Parts III and V, *J.*, 1946, 797, 807; Balfe, Kenyon, and Thain, *J.*, 1952, 790). No systematic study has hitherto been reported of the effect of *ortho*- or *para*-alkyl substituents on the reactivity of such 1-arylmethanols.

It would be expected that inductive and hyperconjugative electron release by the alkyl groups would facilitate unimolecular heterolysis of the alkyl–oxygen bond, as it does of the alkyl–halogen bond in the analogous alkyl halides (Hughes, Ingold, and Taher, *J.*, 1940, 949), *e.g.*:

Evidence supporting this was given by Balfe, Hargreaves, and Kenyon (*J.*, 1951, 375) who showed that 2 : 4′-dimethyldiphenylmethyl hydrogen phthalate was more reactive by a unimolecular alkyl–oxygen fission mechanism than was diphenylmethyl hydrogen phthalate. The introduction in the α-position of alcohols of the 2 : 4 : 6-trimethylphenyl group has been shown to promote alkyl–oxygen heterolysis; for example, a solution of di-(2 : 4 : 6-trimethylphenyl)methanol in concentrated sulphuric acid shows a van't Hoff factor $i = 4{\cdot}04$, indicating the formation of the stable dimesitylcarbonium ion (Deno and Newman, *J. Amer. Chem. Soc.*, 1951, **73**, 3644). 4-Methyldiphenylmethanol and 2 : 4 : 6-trimethyldiphenylmethanol have now been resolved *via* their hydrogen phthalic esters, and the tendency of the alcohols and their esters to undergo unimolecular alkyl–oxygen fission has been investigated.

Earlier workers failed to resolve 4-methyldiphenylmethanol (Cohen, Marshall, and Woodman, *J.*, 1915, **107**, 887; Reis and Schneider, *Z. Krist.*, 1929, **69**, 62), but we find that the brucine salt of the hydrogen phthalate is optically pure after three crystallisations from ethyl acetate. The alcohol, and its hydrogen phthalate, hydrogen succinate, formate, acetate, and benzoate, under mildly acid conditions all undergo reactions characteristic of alkyl–oxygen fission; for example, they alkylate alcohols, phenols, carboxylic acids, sodium toluene-*p*-sulphinate (giving the *p*-tolyl sulphone), and acetyl chloride (giving the alkyl chloride). In all these reactions, the optically active reactant gives inactive products, indicating the presence of carbonium ions as the reaction intermediate. In sodium hydroxide solution, some disproportionation of the hydrogen phthalate occurs, to give the dialkyl phthalate and phthalic acid.

2 : 4 : 6-Trimethyldiphenylmethanol was resolved by fractional crystallisation of the strychnine salt of its hydrogen phthalate from acetone. This alcohol and its hydrogen phthalate display an approximately equal reactivity by a unimolecular alkyl–oxygen

* Part XIII, *J.*, 1954, 779.

fission mechanism to that of the corresponding 4-methyldiphenylmethyl compounds. Under acid conditions they alkylate carboxylic acids, alcohols, thiocresol, sodium toluene-*p*-sulphinate, and acetyl chloride; optically active reactants give racemic products. Hydrolysis of the optically active hydrogen phthalate in aqueous sodium hydroxide of concentration less than 0·5N proceeds with some racemisation, and in 0·3N-aqueous sodium hydroxide at room temperature hydrolysis is accompanied by the formation of some dialkyl phthalate.

Construction of molecular models shows that, whereas the 4-methyldiphenylcarbonium ion may become planar with the incursion of very little deformation of bond angles, the 2 : 4 : 6-trimethyldiphenylcarbonium ion cannot assume a planar configuration. In the latter case, if the mesityl group is coplanar with the bonds about the reaction centre, the phenyl group is forced into a plane almost at right angles to that of the rest of the molecule. Resonance stabilisation of the carbonium ion therefore probably involves only the mesityl group, just as only one mesityl group is involved in the stabilisation of the dimesitylcarbonium ion (Deno and Newman, *loc. cit.*).

Experimental

4-Methylbenzophenone.—A mixture of benzoyl chloride (67 g.) and toluene (67 g.) was added, during 2 hr., to a stirred suspension of aluminium chloride (100 g.) in toluene (150 g.). After 2 hr. at 100°, and 2 days at room temperature, the solution was worked up in the usual manner, giving 4-methylbenzophenone (yield, 90%), as a pale yellow oil, b. p. 310—320°, m. p. 59·5° after crystallisation from light petroleum.

4-Methyldiphenylmethanol.—Zinc dust (85 g.) was added slowly to a stirred solution of the ketone (85 g.) and potassium hydroxide (85 g.) in 96% ethanol (400 c.c.). After 1 hr. at 100°, the solution gave, in almost quantitative yield, 4-methyldiphenylmethanol, as needles, m. p. 51—53°, from light petroleum. The above method of preparation is markedly superior to that involving the Grignard reaction between *p*-bromotoluene and benzaldehyde.

Esters of 4-Methyldiphenylmethanol.—A mixture of the alcohol (83 g.), phthalic anhydride (66 g.), and pyridine (35 g.), after 3 hr. at 45—55°, was diluted with an equal volume of acetone, and decomposed by the addition of a slight excess of dilute hydrochloric acid. Dilution with water gave *4-methyldiphenylmethyl hydrogen phthalate* (125 g.) which separated from ether–light petroleum or from aqueous ethanol as clusters of needles, m. p. 120—122° (Found, by rapid titration with 0·1N-NaOH : equiv., 345. $C_{22}H_{18}O_4$ requires equiv., 346).

A mixture of the alcohol (19·8 g.), succinic anhydride (10 g.), and pyridine (7·7 g.), after 5 hr. at 55—60°, yielded the *hydrogen succinate* (20 g.) as needles from ether–light petroleum; m. p. 100—100·5° (Found : equiv., 301. $C_{18}H_{18}O_4$ requires equiv., 298).

The alcohol (20 g.) in 98% formic acid (30 c.c.) was kept at 100° for 45 min. An ethereal extract yielded the *formate* as needles (from methanol) (20 g.), m. p. 52—53° (Found, by hydrolysis : equiv., 225. $C_{15}H_{14}O_2$ requires equiv., 226). The (−)-alcohol (see below) yielded the (±)-formate.

The (−)-alcohol (4·2 g.), $[\alpha]_D^{22}$ −14·8° (*l*, 2; *c*, 1·34 in CS_2), pyridine (2 g.), and acetic anhydride (2·2 g.), after 5 days, yielded the *acetate* (4·0 g.), b. p. 154—156°/2 mm., $[\alpha]_D^{22}$ −16·8° (*l*, 2; *c*, 2·538 in C_6H_6) (Found, by hydrolysis : equiv., 251. $C_{16}H_{16}O_2$ requires equiv., 240). Similarly the (−)-alcohol (0·5 g.) was heated under reflux in glacial acetic acid (20 c.c.), by which time the solution was optically inactive; the (±)-acetate was isolated (0·585 g.) (Found : equiv., 243).

After 16 hr., a mixture of the alcohol (10 g.), pyridine (4 g.), and benzoyl chloride (6·5 g.) yielded the *benzoate* as clusters of small needles (from ethanol) (15 g.), m. p. 81—82° (Found, by hydrolysis : equiv., 301. $C_{21}H_{18}O_2$ requires equiv., 302).

(+)- and (−)-4-Methyldiphenylmethyl Hydrogen Phthalate.—From a solution of the (±)-hydrogen phthalate (52·5 g.) and brucine (65·2 g.) in ethyl acetate (250 c.c.), the crystalline salt [48 g.; m. p. 119—120° (decomp.)] separated as needles during 21 days. Two further crystallisations from ethyl acetate gave the optically pure brucine salt (22 g.), m. p. 102—105°. Decomposition of this salt gave the (+)-hydrogen phthalate (5 g.), m. p. 114—114·5°, $[\alpha]_D$ +18·5° (*l*, 2; *c*, 1·15 in C_6H_6). No increase in rotatory power was effected by further recrystallisation of the brucine salt of this ester.

Part of the hydrogen phthalate (5·0 g.), $[\alpha]_D$ −9·7° (*l*, 2; *c*, 2·06 in C_6H_6), which was recovered from the first two mother-liquors of brucine salts, was dissolved in ethyl acetate

and added to a suspension of quinidine (4·75 g.) in ethyl acetate (15 c.c.). The clear solution soon deposited the quinidine salt as crystals (7·0 g.), m. p. 145—148°. Recrystallisation gave a salt, m. p. 145—145·5°, which was decomposed to yield the (−)-hydrogen phthalate, m. p. 114—114·5°, $[\alpha]_D$ −16·4° (*l*, 2; *c*, 1·3 in C_6H_6).

(+)-4-*Methyldiphenylmethanol.*—The (+)-hydrogen phthalate (1·5 g.) was dissolved in a solution of sodium (0·7 g.) and water (1 c.c.) in absolute ethanol (100 c.c.); after 15 min. at 100°, sodium phthalate separated. Addition of water gave (+)-4-methyldiphenylmethanol (0·7 g.) as a crystalline precipitate, m. p. 61—63°, $[\alpha]_D$ +26·9° (*l*, 2; *c*, 1·378 in CS_2). Cohen, Marshall, and Woodman (*loc. cit.*) were unable to resolve 4-methyldiphenylmethanol *via* its hydrogen phthalate They therefore resolved 4-methyldiphenylmethylamine by crystallisation of its bromocamphorsulphonate and, on treatment of the apparently optically pure amine hydrochloride with sodium nitrite, obtained the partially active alcohol, $[\alpha]_D^{20}$ −1·4° (*l*, 2; *c*, 8·904 in ethanol).

Reactions of 4-*Methyldiphenylmethanol.*—(i) *With sodium toluene*-p-*sulphinate.* After 1 hr., a solution of the alcohol (1·7 g.) and sodium toluene-*p*-sulphinate (2·0 g.) in formic acid (50 c.c., 98—100%) gave 4-*methyldiphenylmethyl* p-*tolyl sulphone* (2·0 g.), m. p. 159—160°, in quantitative yield (Found : S, 9·5. $C_{21}H_{20}O_2S$ requires S, 9·5%). Similarly, when the alcohol (0·633 g.) and toluene-*p*-sulphinic acid (0·516 g.) were boiled with water (15 c.c.), the sulphone was isolated quantitatively.

(ii) *With methanol.* The alcohol was recovered unchanged after 30 hours' heating under reflux in anhydrous or 25% aqueous methanol, but in the presence of 0·5N-hydrochloric acid, it was converted during 16 hr. into the (±)-methyl ether, b. p. 160—165°/10 mm., in quantitative yield.

(iii) *With hydrochloric acid and acetyl chloride.* The alcohol (5·0 g.) was triturated with cold concentrated hydrochloric acid (50 c.c.). The oil which was immediately formed was left for 12 hr. in a vacuum-desiccator, and distilled, yielding 4-methyldiphenylmethyl chloride (5·1 g.), b. p. 160—164°/6—7 mm., n_D^{24} 1·5865 (Found : Cl, 16·3. Calc. for $C_{14}H_{13}Cl$: Cl, 16·4%). The reaction of acetyl chloride alone similarly yielded the chloride, but in the presence of pyridine gave the acetate, b. p. 190—194°/10—12 mm. (Found, by hydrolysis : equiv., 242).

Reactions of 4-*Methyldiphenylmethyl Esters.*—(i) *With sodium toluene*-p-*sulphinate.* A solution of the hydrogen phthalic ester (2·0 g.) and sodium toluene-*p*-sulphinate (1·23 g.) in 0·3N-sodium hydroxide (19 c.c.) deposited crystals of the sulphone (1·8 g.) during 12 days. Recrystallisation from acetic acid gave 4-methyldiphenylmethyl *p*-tolyl sulphone as very small needles, m. p. 159—160° (Found, S, 9·5. Calc. for $C_{21}H_{20}O_2S$: S, 9·5%). The (−)-hydrogen phthalate gave the (±)-sulphone. Under similar conditions, the hydrogen succinate also gave the sulphone, in 78% yield. The formate, acetate, and benzoate reacted with sodium toluene-*p*-sulphinate at room temperature in formic acid solution, but not in acetic acid solution, to give the sulphone. The same (±)-sulphone was obtained in excellent yield when the hydrogen phthalate, formate, benzoate, or (−)-acetate was heated under reflux for 15 min. with an aqueous solution of toluene-*p*-sulphinic acid.

(ii) *With methanol.* The hydrogen phthalic ester (3·0 g.) was heated under reflux with anhydrous methanol (40 c.c.) for 40 hr., yielding phthalic acid (0·62 g.; m. p. 188—190°) (Found : equiv., 83. Calc. for $C_8H_6O_4$: equiv., 83) and methyl 4-methyldiphenylmethyl ether (0·7 g.; b. p. 150—154°/8 mm.) (Found : C, 85·6; H, 7·2. Calc. for $C_{15}H_{16}O$: C, 84·9; H, 7·5%). Under similar conditions, the (−)-hydrogen phthalate yielded the inactive ether. Likewise, the hydrogen succinate was converted into the methyl ether. The acetate and benzoate were recovered from anhydrous methanol, and in 14—28% aqueous methanol underwent partial hydrolysis. From solution in methanol containing 14% of 0·5N-aqueous hydrochloric acid, after boiling for 12 hr., the methyl ether was isolated in excellent yield. However, the formate, after 24 hr. in boiling anhydrous methanol, was converted quantitatively into the alcohol, and from neutral or acidic aqueous methanol gave the methyl ether.

(iii) *With phenol.* The hydrogen phthalate (3·5 g.) and phenol (1·0 g.) were heated under reflux in dry chloroform. Phthalic acid (1·42 g.), m. p. 195° (decomp.) (Found : equiv., 82), was precipitated during 20 hr. The filtrate yielded 4-*methyldiphenylmethyl phenyl ether* (2·49 g.), b. p. 190—200°/7 mm., n_D^{20} 1·5910 (Found : C, 87·0; H, 6·8. $C_{20}H_{18}O_4$ requires C, 87·5; H, 6·5%).

(iv) *With carboxylic acids.* The hydrogen phthalate (3·0 g.), dissolved in 90% formic acid, after 15 min. at 100°, yielded 4-methyldiphenylmethyl formate (1·9 g., from methanol,), m. p. 50—52°, mixed m. p. with 4-methyldiphenylmethanol, 40—44° (Found : C, 79·7; H, 6·1. Calc. for $C_{15}H_{14}O_2$: C, 79·6; H, 6·2%). The (−)-hydrogen phthalate gave the (±)-formate.

During 3 months, the hydrogen phthalate reacted with cold glacial acetic acid to yield 4-methyldiphenylmethyl acetate (1·38 g.). The hydrogen succinate (1·0 g.) in 98% formic acid (10 c.c.), after 2 days at room temperature, gave the formate in 90% yield; in acetic acid, reaction was incomplete (30%) after 3 months at room temperature, but after 24 hours' heating under reflux the acetate was isolated in 69% yield.

The (−)-acetate (0·68 g.) in 98% formic acid (20 c.c.), after 5 days, yielded the (±)-formate (0·63 g.), m. p. 50—52°. The benzoate (0·82 g.) dissolved in 98% formic acid (10 c.c.) on gentle warming; next day it yielded the formate (0·6 g.), m. p. and mixed m. p. 51—52°. On being heated under reflux in glacial acetic acid (10 c.c.) for 24 hr., the benzoate (0·73 g.) was converted into the acetate (0·57 g.) (Found: equiv., 239).

(v) *With hydrochloric acid.* The hydrogen phthalate (1·0 g.) was triturated with concentrated hydrochloric acid (10 c.c.). After 12 hr., an oil had separated, which was extracted with ether, yielding 4-methyldiphenylmethyl chloride (0·22 g.), b. p. 160—166°/7 mm., n_D^{25} 1·5864 (Found: Cl, 16·3%). The aqueous layer yielded phthalic acid (0·31 g.), m. p. 190° (decomp.). The hydrogen phthalate was recovered after solution in acetyl chloride for 6 days. The acetate (0·50 g.), on trituration with concentrated hydrochloric acid (10 c.c.), was similarly converted into the chloride (0·44 g.), b. p. 160—165°/7 mm. (Found: Cl, 16·9%).

(vi) *With aqueous sodium hydroxide.* Solutions of the hydrogen phthalate or hydrogen succinate in 0·1—0·3N-sodium hydroxide yielded the alcohol in *ca.* 90% yield after a few days. Under the following conditions, however, some disproportionation occurred, giving the neutral ester. The hydrogen phthalate (1·0 g.) in 0·1N-sodium hydroxide (34 c.c.), after 2·5 hr. at 65°, yielded an oil which, from methanol, gave 4-methyldiphenylmethanol (0·2 g.), m. p. 50°, and impure di-(4-methyldiphenylmethyl) phthalate (0·34 g.), as a viscous oil which could not be crystallised (Found, by hydrolysis: equiv., 259. Calc. for $C_{36}H_{30}O_4$: equiv., 263). Disproportionation also occurred when the hydrogen phthalate (3·0 g.) was heated under reflux in chloroform (50 c.c.) for 34 hr.; the hydrogen phthalate (0·63 g.), m. p. 120—122°, phthalic acid (0·53 g.), m. p. 190° (decomp.), and the neutral phthalate (1·5 g.) (Found, by hydrolysis: equiv., 255) were isolated. The hydrogen succinate (1·0 g.) in 0·1N-sodium hydroxide (40 c.c.) after 6 days yielded an oil (0·294 g.) which did not solidify. From the aqueous layer, the hydrogen succinate (0·6 g.), m. p. 98—100°, was recovered. The oil was identified as *di-(4-methyldiphenylmethyl) succinate* by quantitative hydrolysis (Found: equiv., 244. $C_{32}H_{30}O_4$ requires equiv., 239), from which the alcohol (0·07 g.), m. p. 50—52°, was isolated.

2 : 4 : 6-*Trimethyldiphenylmethanol.*—The Grignard reaction between bromomesitylene (20 g.), magnesium (2·4 g.), and benzaldehyde (10·5 g.) gave 2 : 4 : 6-trimethyldiphenylmethanol (18 g.), which was purified through its hydrogen phthalate.

(±)-2 : 4 : 6-*Trimethyldiphenylmethyl Hydrogen Phthalate.*—A mixture of the unpurified alcohol (18 g.), phthalic anhydride (12 g.), and pyridine (6·5 g.) in benzene (13 c.c.), after 2 hr. at 60—65° and 16 hr. at room temperature, yielded 2 : 4 : 6-*trimethyldiphenylmethyl hydrogen phthalate* (27 g., 90%) as rhombs (from ether–light petroleum), m. p. 159—160° (Found: equiv., 375. $C_{24}H_{21}O_4$ requires equiv., 374). From chloroform the hydrogen phthalate gave efflorescent crystals containing about 1 mol. of chloroform, which melted first at 89—92° (decomp.) and then resolidified and melted again at 158—160°.

(+)-2 : 4 : 6-*Trimethyldiphenylmethyl Hydrogen Phthalate.*—A warm solution of the (±)-hydrogen phthalate (80 g.) and strychnine (69 g.) in acetone (200 c.c.) overnight deposited the crystalline salt (65 g.). After 5 recrystallisations from acetone this salt (35 g.), m. p. 138—141° (decomp.), was decomposed with aqueous ammonia, yielding the (+)-hydrogen phthalate, m. p. 125—126° (from benzene), $[\alpha]_D^{20}$ +89·1° (*l*, 1; *c*, 3·74 in $CHCl_3$). The m. p. and rotatory power of this ester were unchanged on further recrystallisation.

(+) *and* (−)-2 : 4 : 6-*Trimethyldiphenylmethanol.*—The above (+)-hydrogen phthalate (10 g.) was dissolved in a solution of sodium (3·5 g.) and water (5 c.c.) in ethanol (150 c.c.); after 15 min. at 100°, sodium phthalate separated. Addition of water gave (+)-2 : 4 : 6-trimethyldiphenylmethanol (5·7 g.), m. p. 67—69°. Recrystallisation from light petroleum yielded the *alcohol* in large prisms (4·5 g.), m. p. 70—70·5°, $[\alpha]_D^{20}$ +148·8° (*l*, 2; *c*, 1·250 in $CHCl_3$) (Found: C, 85·1; H, 8·0. $C_{16}H_{18}O$ requires C, 85·0; H, 8·0%). From this alcohol, the (+)-hydrogen phthalate was regenerated, having m. p. 125—126°, $[\alpha]_D^{19}$ +88·7° (*l*, 1; *c*, 2·57 in $CHCl_3$). The hydrogen phthalate from the mother-liquors of brucine salts was crystallised from ether–light petroleum, and the (±)-ester slowly separated. The oily (−)-hydrogen phthalate from the filtrate was hydrolysed, yielding (−)-2 : 4 : 6-trimethyldiphenylmethanol (10 g.; from light petroleum), m. p. 70—70·5°, $[\alpha]_D^{20}$ −147·9° (*l*, 2; *c*, 1·305 in $CHCl_3$).

(±)-, (+)-, *and* (−)-2 : 4 : 6-*Trimethyldiphenylmethyl Benzoate*.—The (±)-alcohol reacted with benzoyl chloride in the presence of pyridine to give the (±)-benzoate in 90% yield, as shining needles, m. p. 93—94°. Louise (*Ann. Chim. Phys.*, 1885, **6**, 209) reports m. p. 92°. Similarly, the (+)-alcohol gave the (+)-benzoate, m. p. 79—80°, $[\alpha]_D^{20}$ +44·8° (*l*, 2; *c*, 1·280 in C_6H_6), and the (−)-alcohol gave the (−)-benzoate, $[\alpha]_D^{18}$ −44·3° (*l*, 2; *c*, 2·008 in C_6H_6).

Reactions of 2 : 4 : 6-*Trimethyldiphenylmethanol*.—(i) *With sodium toluene*-p-*sulphinate*. A mixture of the alcohol (2·25 g.) and sodium toluene-*p*-sulphinate (2·15 g.) in acetic acid (40 c.c.) containing concentrated sulphuric acid (0·5 c.c.) was heated on the steam-bath for 30 min. and rapidly became purple. Nexy day, water was added, and p-*tolyl* 2 : 4 : 6-*trimethyldiphenylmethyl sulphone* (3·3 g.) was isolated as needles (from ethanol), m. p. 147—148° (Found : C, 75·5; H, 6·8; S, 8·8. $C_{23}H_{24}O_2S$ requires C, 75·8; H, 6·7; S, 8·8%). The same reagents in formic acid solution, in the absence of sulphuric acid, similarly yielded the sulphone.

(ii) *With acids*. The alcohol (5 g.), after being heated under reflux with 50% sulphuric acid (100 c.c.) for 2 days, yielded di-(2 : 4 : 6-trimethyldiphenylmethyl) ether, m. p. 137—138° (from ether–light petroleum). Louise (*loc. cit.*) records m. p. 137°. After 1·5 days in boiling acetic acid solution (20 c.c.), the (+)-alcohol (0·55 g.) was converted into the (±)-acetate (0·50 g.), b. p. 136—138°/0·8 mm., which could not be solidified (Found : C, 80·7; H, 7·7. Calc. for $C_{18}H_{20}O_2$: C, 80·6; H, 7·5%). Louise (*loc. cit.*) reports m. p. 52°. After 16 hr. at room temperature, a solution of the (+)-alcohol (1·0 g.) in 98% formic acid (8 c.c.) gave the *formate* (1·1 g.), m. p. 66·5—67·5° (Found : C, 80·1; H, 7·1. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%). The (+)-alcohol (0·5 g.) was heated on the steam-bath for 5 min. with trichloroacetic acid (1·0 g.), and gave 2 : 4 : 6-*trimethyldiphenylmethyl trichloroacetate* (90%), m. p. 92—93° (Found : C, 58·4; H, 4·7; Cl, 29·5. $C_{18}H_{17}O_2Cl_3$ requires C, 58·2; H, 4·6; Cl, 28·4%).

(iii) *With acetyl chloride*. Acetyl chloride (2 c.c.) was added to the (+)-alcohol (0·5 g.) which dissolved rapidly, giving a deep purple solution. The (±)-*chloride* (0·34 g.) was isolated, having b. p. 138—140°/0·8 mm. (Found : C, 78·5; H, 7·3; Cl, 14·1%; equiv., by hydrolysis, 246. $C_{18}H_{17}Cl$ requires C, 78·5; 7·0; Cl, 14·5%; equiv., 245). From the hydrolysate, ethyl 2 : 4 : 6-trimethyldiphenylmethyl ether was isolated, m. p. 29—30°.

Reactions of 2 : 4 : 6-*Trimethyldiphenylmethyl Esters*.—(i) *With sodium toluene*-p-*sulphinate*. A solution of the hydrogen phthalate (2·0 g.) and sodium toluene-*p*-sulphinate (1·1 g.) in aqueous sodium hydroxide (25 c.c. of 0·2N), after 2 days at 50° deposited the *p*-tolyl sulphone which, recrystallised (from ethanol; 1·7 g.), had m. p. 147—148°. The (+)-ester gave the (±)-sulphone.

(ii) *With thio*-p-*cresol*. A solution of the hydrogen phthalate (3·5 g.) in acetone (15 c.c.) was added to a suspension of thio-*p*-cresol (1·15 g.) in formic acid (7 c.c.). Within a few minutes, phthalic acid (1·2 g.) was deposited. Next day, water was added to the solution, yielding p-*tolyl* 2 : 4 : 6-*trimethyldiphenylmethyl sulphide* (3 g.), which separated from acetic acid or ethanol as leaflets, m. p. 93—94° (Found : C, 82·8; H, 7·1; S, 10·0. $C_{23}H_{24}S$ requires C, 83·1; H, 7·2; S, 9·7%). The (+)-ester gave the (±)-sulphide. A solution of the sulphide (1·0 g.) in acetic acid (15 c.c.) containing hydrogen peroxide (4·0 c.c. of 90-vol.), after 9 hr. at 60°, on cooling deposited *p*-tolyl 2 : 4 : 6-trimethyldiphenylmethyl sulphone, m. p. 145—147°, undepressed on admixture with the specimen prepared from sodium toluene-*p*-sulphinate.

(iii) *With ethanol*. A solution of the (+)-hydrogen phthalate (0·5 g.) in 96% ethanol (40 c.c.) was heated under reflux for 20 hr., by which time it was optically inactive. (±)-Ethyl 2 : 4 : 6-trimethyldiphenylmethyl ether (0·2 g.), b. p. 131—133°/0·5 mm., m. p. 30—31°, was isolated (Found : C, 85·0; H, 8·8. Calc. for $C_{18}H_{22}O$: C, 85·0; H, 8·8%). Louise (*loc. cit.*) reports m. p. 32°. The benzoate (2 g.) was recovered after being heated under reflux in 96% ethanol (20 c.c.) for 56 hr., but the formate, after 6 hours' heating or 6 weeks at room temperature, gave the ethyl ether in 80% yield.

(iv) *With carboxylic acids*. A solution of the (+)-hydrogen phthalate (0·38 g.) in 98% formic acid (10 c.c.) rapidly became turbid. After 15 min. the solution was diluted with ice-cold sodium hydroxide solution, yielding (±)-2 : 4 : 6-trimethyldiphenylmethyl formate (0·2 g.), m. p. and mixed m. p. 66—67°. The (+)-hydrogen phthalate (2 g.) in acetic acid (20 c.c.) after 5 hr. at 100° gave the (±)-acetate (1·0 g.), b. p. 135—136°/0·6 mm. A mixture of the (+)-hydrogen phthalate (0·3 g.) and trichloroacetic acid (0·5 g.) was ground with gentle heating, forming a thick slurry which changed to a purple semi-solid. After 5 min. at 100°, aqueous sodium hydroxide was added, yielding (±)-2 : 4 : 6-trimethyldiphenylmethyl trichloroacetate (from light petroleum; 0·25 g.), m. p. and mixed m. p. 92—93°.

(v) *With acetyl chloride*. A solution of the (+)-hydrogen phthalate (2·0 g.) in acetyl chloride (1·0 c.c.) rapidly set to a purple semi-solid. After being kept overnight *in vacuo* over

potassium hydroxide, a light petroleum extract yielded, on distillation, (±)-2 : 4 : 6-trimethyldiphenylmethyl chloride (0·6 g.), b. p. 138—140°/0·8 mm.

(vi) *With aqueous sodium hydroxide.* Solutions of the (+)-hydrogen phthalate (0·6 g.) in aqueous sodium hydroxide (10 mols.) of various concentrations were heated on the steam-bath for 5 min. and the liberated alcohol was isolated by extraction with light petroleum. The following results were obtained :

NaOH, N	2	1	0·5	0·25
Optical purity of alcohol, %	100	98·5	88·1	81·7

Under milder conditions, some neutral phthalate was also formed as an oil which could not be purified. A solution of the (+)-hydrogen phthalate (1·9 g.) ($[\alpha]_D^{20}$ +89·2° in $CHCl_3$) in aqueous sodium hydroxide (15·7 c.c. of 0·3N), after 8 hr. at 60°, deposited a neutral oil (1·3 g.), $[\alpha]_D^{20}$ +70·0° (*l*, 1; *c*, 1·46 in $CHCl_3$), which, by quantitative hydrolysis, was shown to consist of 81% of the dialkyl phthalate and 19% of the alcohol. Hydrolysis of this mixture of neutral phthalate and alcohol with sodium ethoxide in ethanol gave the alcohol possessing 68·5% of its maximum optical activity.

Thanks are expressed to Imperial Chemical Industries Limited for a grant.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, May 15th*, 1954.]

The Alkaloids of Picralima nitida, *Stapf, Th. and H. Durand. Part I. The Structure of Akuammigine.*

By SIR ROBERT ROBINSON and A. F. THOMAS.

[Reprint Order No. 5410.]

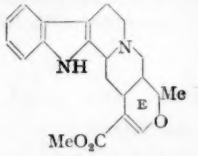
Akuammigine, an alkaloid from *Picralima nitida*, Stapf, has been shown to be an indole derivative containing the group, $MeO_2C{\cdot}C{:}C{\cdot}O$. Dehydrogenation with selenium affords alstyrine, and it is suggested that the substance is a stereoisomeride of δ-yohimbine.

EXTRACTS of *Picralima nitida*, Stapf (syn. *P. Klaineana*, Pierre) are employed by West African natives because of their alleged antipyretic and antimalarial properties, also as a remedy for chest complaints and as a fish poison. The drug has various local names, but apparently not " akuamma " (cf. Henry and Sharp, *J.*, 1927, 1950), a term used to denote the fruit of *Pentaclethra macrophylla*, Benth., and later extended to the *Picralima* extract in Accra (Dalziel, " The Useful Plants of West Tropical Africa, H.M.S.O., London, 1937, p. 220).

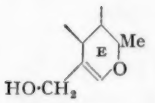
After the alkaloids had been shown to be inactive in avian and human malaria (Goodson, Henry, and Macfie, *Biochem. J.* 1930, **24**, 874; van den Branden, *Ann. Soc. Belg. Med. trop.*, 1930, **10**, 123), detailed chemical research on them was not pursued. A series of papers on the remarkable pharmacological properties of some of the alkaloids is due to Raymond-Hamet (a summary of these is to be found in *Rev. Int. Bot. app. Agric. trop.*, 1951, **31**, 465). Akuammigine, however, was found to be almost devoid of physiological activity (Raymond-Hamet, *Compt. rend.*, 1945, **221**, 699).

Akuammigine was first isolated by Henry (*J.*, 1932, 2759), and the formula was given as $C_{22}H_{26}O_3N_2$, which we propose to alter to $C_{21}H_{24}O_3N_2$. The presence of a methoxyl group, and absence of a methylimino-group have been confirmed. The ultra-violet spectrum is like that of a true aromatic indole (Raymond-Hamet, *loc. cit.*), with the flattening associated with $MeO_2C{\cdot}C{:}C{\cdot}O$ (Bader, *Helv. Chim. Acta*, 1935, **36**, 215; Millson, Robinson, and Thomas, *Experientia*, 1953, **9**, 89), and the infra-red spectrum has been shown to contain peaks due to the presence of OH (as water of crystallisation), C=O (unsaturated ester type) and C=C, with an extra peak in the carbonyl absorption region (Millson *et al.*, *loc. cit.*). This extra peak has now been shown to be caused by intramolecular hydrogen bonding, since it is not observed in the spectrum of a chloroform solution. Akuammigine has been said to resemble mayumbine (I) (Janot, Goutarel, and Massonneau, *Compt. rend.*, 1952, **234**, 850) on the ground that it contains one *C*-methyl group, unlike the α-type indole alkaloids with an alicyclic E-ring (Raymond-Hamet, *loc. cit.*). This fact has

been confirmed, although values of about 120% are found in the Kuhn–Roth determination. A similar discrepancy was noted in the case of tetrahydroalstonine (Elderfield and Gray, *J. Org. Chem.*, 1951, **16**, 506).



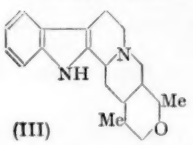
(I)



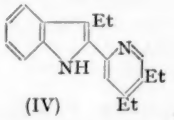
(II)

The presumed ester group of akuammigine is not readily hydrolysed by alkali, a fact which tallies with the usual behaviour of dihydropyran esters of the alstonine type (Bader, *loc. cit.*; Schlittler and Hohl, *Helv. Chim. Acta*, 1952, **35**, 29). Reduction with lithium aluminium hydride gave an alcohol, akuammigol (II), corresponding to the tetrahydroalstonol obtained by Elderfield and Gray from tetrahydroalstonine (*loc. cit.*); this substance retains solvents of crystallisation tenaciously, and, again like tetrahydroalstonol, gives no crystalline salts with acids although, unlike the latter, both a methiodide and a normal *O*-acetate could be obtained.

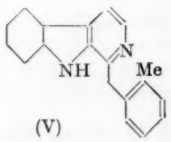
Catalytic hydrogenation of dihydropyran esters is known to be difficult (cf. Bader, *loc. cit.*), and hydrogenation of akuammigol could not be effected under conditions similar to those used by Elderfield and Gray (*loc. cit.*) in the case of tetrahydroalstonine. A product in the latter example was a substance, $C_{20}H_{26}ON_2$, presumably (III) and possibly the result of rearrangement and hydrogenolysis of (II). Furthermore no reaction was observed when akuammigol was treated with sodium in liquid ammonia.



(III)



(IV)



(V)

Selenium dehydrogenation of akuammigine gave alstyrine (IV), identified with a specimen from corynantheine (Karrer and Enslin, *Helv. Chim. Acta*, 1949, **32**, 1390; Janot and Goutarel, *Bull. Soc. chim.*, 1951, 588). This supports the formulation of akuammigine as a stereoisomeride of δ-yohimbine, since alicyclic α-type indole alkaloids give yobyrine (V) on dehydrogenation with selenium (Le Men, *Compt. rend.*, 1952, **234**, 1559). The known alkaloids to which structure (I) has been attributed are shown in the accompanying table.

δ-Yohimbine and its Stereoisomerides.

Alkaloid	Source	Reference: isolation	structure
δ-Yohimbine	*Pausinystalia yohimba*	1	2
(Ajmalicine)	*Rauwolfia serpentina*	3	4
	Reduction of serpentine from *R. serpentina*	5	5, 4
Tetrahydroalstonine	Reduction of alstonine from *Alstonia constricta*	6	7
	Pyrolysis of melinonine-A from *Strychnos melinoniana*	8	8
Mayumbine	*Pseudocinchona mayumbensis*	9	10
Akuammigine	*Picralima nitida*	11	12

References: 1, Heinemann, *Ber.*, 1934, **67**, 15. 2, Goutarel and Le Hir, *Bull. Soc. chim.*, 1951, 909. 3, Popelak, Spingler, and Kaiser, *Naturwiss.*, 1953, **40**, 625. 4, Weisenborn, Moore, and Diassi, *Chem. and Ind.*, 1954, 375; Hofmann, *Helv. Chim. Acta*, 1954, **37**, 849; Klohs, Draper, Keller, Malesh, and Petracek, *J. Amer. Chem. Soc.*, 1954, **76**, 1332. 5, Schlittler and Schwarz, *Helv. Chim. Acta*, 1950, **33**, 1463. 6, Sharp, *J.*, 1938, 1353. 7, Elderfield and Gray, *J. Org. Chem.*, 1951, **16**, 506. 8, Schlittler and Hohl, *Helv. Chim. Acta*, 1952, **35**, 29. 9, Raymond-Hamet, *Compt. rend.*, 1951, **232**, 2354. 10, Janot, Goutarel, and Massonneau, *ibid.*, 1952, **234**, 850. 11, Henry, *J.*, 1932, 2759. 12. Present communication.

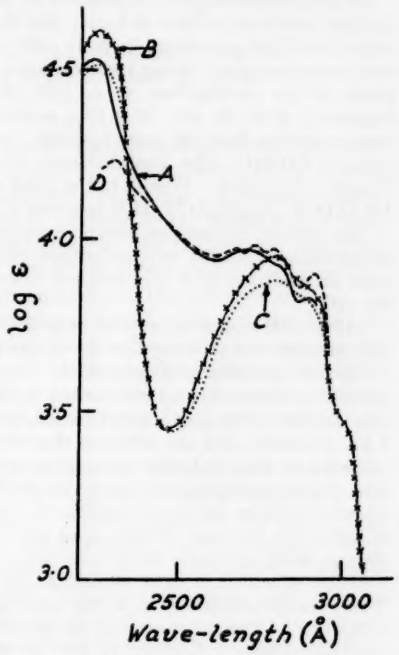
Experimental

Akuammigine hydrochloride was obtained as the least soluble fraction during extraction of the crude alkaloid mixture with N-hydrochloric acid (Henry, *loc. cit.*). It crystallises from aqueous methanol as colourless prisms, m. p. 285—290° (decomp.; dependent on the rate of heating), $[\alpha]_D^{23}$ −44° (*c*, 0·7 in MeOH) (Found: C, 64·8, 64·7, 64·9; H, 6·6, 6·5, 6·4; N, 7·0, 7·2;

Cl, 9·4, 9·2; OMe, 8·1; NMe, 1·1; *C*-Me, 4·9, 4·5. $C_{21}H_{24}O_3N_2$,HCl requires C, 64·8; H, 6·5; N, 7·2; Cl, 9·1; 1OMe, 8·0; 1*C*-Me, 3·9%).

Akuammigine crystallised from aqueous ethanol as colourless square plates, m. p. 113°, $[\alpha]_D^{18·5}$ −42° (*c*, 1·6 in EtOH), +1° (*c*, 2·4 in pyridine), pK_a 6·58 (Found: C, 68·0; H, 7·1; N, 7·5. $C_{21}H_{24}O_3N_2,H_2O$ requires C, 68·1; H, 7·0; N, 7·6%). Attempted removal of the solvent caused decomposition. A solution of akuammigine in chloroform slowly decomposes in air, but a solution in aqueous alcohol is stable. Henry (*loc. cit.*; 1932) gives the m. p. 127° for akuammigine but we found the lower value cited, unchanged after several recrystallisations, and rather sharp.

The *hydrobromide* separated when a hot, concentrated solution of potassium bromide was added to a saturated solution of the hydrochloride in boiling water; it was recrystallised with difficulty from water, forming colourless prisms, m. p. 248—250° (decomp.) (Found: C, 58·1; H, 5·8; Br, 19·1. $C_{21}H_{24}O_3N_2$,HBr requires C, 58·2; H, 5·8; Br, 18·5%). The *perchlorate* crystallised from water in clusters of needles, m. p. 75° (air-dry), m. p. 204° (dry; decomp.); $[\alpha]_D^{19}$ −39° (*c*, 1·1 in EtOH) [Found, in material dried at 120°/0·005 mm. for 15 hr. (loss, 10·6): C, 55·4; H, 5·7; N, 6·2; Cl, 7·6. $C_{21}H_{24}O_3N_2,HClO_4,3H_2O$ requires $3H_2O$, 10·7; $C_{21}H_{24}O_3N_2,HClO_4$ requires C, 55·7; H, 5·6; N, 6·2; Cl, 7·5%]. The *picrate* separated from ethanol as bright yellow rods of the *monohydrate*, m. p. 173° (Found: C, 53·8; H, 5·1; N, 11·4. $C_{21}H_{24}O_3N_2,C_6H_3O_7N_3,H_2O$ requires C, 54·0; H, 5·0; N, 11·7%). This salt is sometimes obtained in the same way as anhydrous pale yellow rods, m. p. 240° (decomp.) (Found: C, 55·7 H, 4·8; N, 12·2. $C_{21}H_{24}O_3N_2,C_6H_3O_7N_3$ requires C, 55·7; H, 4·8; N, 12·0%)



A, *Akuammigine.*
B, *Akuammigol.*
C, *Akuammigol acetate.*
D, *Mayumbine* (*Raymond-Hamet*, Compt. rend., 1951, **232**, 2354).

Akuammigine and all its salts and derivatives give a bright yellow colour with concentrated nitric acid. No colour is developed by ferric chloride in very dilute hydrochloride acid solution. The Adamkiewicz–Hopkins–Cole reaction (carried out according to Brustlier, Bourbon, and Vignes, *Bull. Soc. chim.*, 1950, 113) give a violet colour (indole reaction).

Akuammigine was not hydrolysed by 10% potassium hydroxide in methanol in 1 hr., nor was any change observed when it was heated with 2 : 4-dinitrophenylhydrazine in ethanolic hydrochloric acid for 1 hr. (contrast the behaviour of alstonine, Elderfield, and Gray, *loc. cit.*).

Reduction of Akuammigine with Lithium Aluminium Hydride.—Akuammigine (200 mg.) was reduced with lithium aluminium hydride (200 mg.) in ether (60 c.c.) for 2 hr. on the steam-bath. Excess of the reagent was decomposed with moist ether, and the filtered solution evaporated until crystallisation started. Akuammigol was recrystallised from ether as flattened rods of the *hemihydrate*, m. p. 211—213° (Found: C, 72·0; H, 7·8; N, 8·4. $C_{20}H_{24}O_2N_2,\frac{1}{2}H_2O$ requires C, 72·0; H, 7·6; N, 8·3%). *Akuammigol* separated from chloroform in crystals with $\frac{1}{3}$ molecule of the solvent, then having m. p. *ca.* 170°, solidifying at once and remelting at 213° (decomp.), $[\alpha]_D^{18}$ −60° (calc. on solvent-free base) [Found: C, 67·3, 66·9; H, 6·9, 6·8; N, 7·9; Cl, 9·4. $(C_{20}H_{24}O_2N_2)_3,CHCl_3$ requires C, 67·0; H, 7·6; N, 7·7; Cl, 9·7%]. After drying to constant weight (120°/0·005 mm. for 5 hr.) the substance still contained about 5·7% of chloroform (Found: C, 70·0; H, 7·2; N, 7·9%) and, to show that it was not a hydrochloride, a potentiometric titration was carried out against 0·1N-hydrochloric acid; this gave pK_a 7·04. Akuammigol dissolves in hot pyridine, but crystallises almost immediately with $1C_5H_5N$, and the pyridine is not lost at 120°/0·01 mm. during 5 hr. Thus dried, it had m. p. 175° (smell of pyridine), remelting at 213° (decomp.) (Found: C, 74·1; H, 7·1; N, 10·3. $C_{20}H_{24}O_2N_2,C_5H_5N$ requires C, 74·4; H, 7·2; N, 10·4%).

Akuammigol methiodide was made from its generators in ethanol and separated as clusters of colourless prisms. After being washed with ethanol, and ether, and dried, it had m. p. 282—284° (decomp.; dependent on rate of heating) (Found: C, 53·2; H, 6·0; I, 28·2. $C_{20}H_{24}O_2N_2,CH_3I,\frac{1}{2}H_2O$ requires C, 53·1; H, 5·9; I, 27·7%).

Attempts to prepare the hydrochloride of akuammigol in various ways afforded only oils.

O-*Acetylakuammigol*.—A solution of akuammigol (200 mg.) in dry pyridine (5 c.c.) and redistilled acetic anhydride (0·5 c.c.) was heated on the steam-bath for 2 min. The mixture was cooled and light petroleum (b. p. 40—60°) added until crystallisation began. In this way, crude acetylakuammigol (120 mg.) was obtaned. After recrystallisation from ether, it was obtained as plates of the *pentahydrate*, m. p. 155° (Found: C, 58·2; H, 7·6; N, 5·9. $C_{22}H_{26}O_3N_2,5H_2O$ requires C, 57·9; H, 8·0; N, 6·1%), or sometimes as needles of a monohydrate, m. p. 155°, which were never free from the pentahydrate; $[\alpha]_D^{19}$ for the pentahydrate was −59° (*c*, 1·2 calc. on dry base, in EtOH). The pentahydrate, when dried to constant weight, gave the *monohydrate* (Found: loss 18·5. Found, in the dried sample: C, 69·2; H, 7·2. $C_{22}H_{26}O_3N_2,5H_2O$ requires $4H_2O$,18·7. $C_{22}H_{26}O_3N_2,H_2O$ requires C, 68·7; H, 7·3%).

No uptake of the gas was observed on shaking akuammigol under hydrogen in aqueous methanol (50%) with 10% palladised charcoal or with glacial acetic acid and Adams catalyst, even on addition of a few drops of concentrated hydrochloric acid (cf. Elderfield and Gray, *loc. cit.*

After attempted reduction with sodium in liquid ammonia, in the presence of alcohol, akuammigol was recovered to the extent of 90% after 1 hr.

Dehydrogenation of Akuammigine with Selenium.—A mixture of akuammigine (450 mg.) with powdered selenium (1 g.) was heated at 250° (metal-bath), and the temperature raised during 15 min. to 280°; the product was cooled, mixed with clean sand, and extracted with methanol for 4 hr. (Soxhlet), and the solution thus obtained was mixed with that of the red oil, which had collected in the condenser during the reaction, in benzene–methanol. The combined extracts were concentrated *in vacuo*, and the residue dissolved in chloroform (25 c.c.), washed twice with aqueous sodium hydrogen carbonate (10%), dried, and evaporated to dryness. The oil was dissolved in benzene (10 c.c.) and passed through an alumina column, the first two fractions (50 c.c. each) of eluate being collected. From these fractions, an orange oil was obtained, the solution of which in light petroleum (b. p. 40—60°) slowly deposited crystals (34 mg.) at 0°. Three recrystallisations from the same solvent gave four- and six-sided plates (21 mg.), m. p. 116—117°. The infra-red and ultra-violet spectra of these crystals were identical with those of alstyrine (Found: C, 81·9; H, 7·7; N, 10·4. Calc. for $C_{19}H_{22}N_2$: C, 82·0; H, 8·0; N, 10·1%). We are very grateful to Professor P. Karrer for a specimen of corynanthyrine (*syn.* alstyrine). From the mother-liquors of these fractions, the picrate, m. p. 210—212°, was obtained, though in very small amount.

Infra-red data (*Nujol suspension unless otherwise stated*).

	Maxima ($cm.^{-1}$)	Interpretation
Akuammigine	3546	OH and NH bands
	3333	
	3049	
	1707	
	1683	Conjugated ester C=O
	1629	Asymmetric C=C (conjugated)
	741	1 : 2-Disubstituted benzene ring
,, in $CHCl_3$	1689	Conjugated ester C=O
	1621	Asymmetric C=C (conjugated)
Akuammigol ($+\frac{1}{2}CHCl_3$)	3195	OH and NH bands
	3049	
	1656	Asymmetric C=C (unconjugated)
	738	1 : 2-Disubstituted benzene ring
Akuammigol acetate	3356	(broad) OH and NH absorption
monohydrate	1712	Unconjugated ester C=O
	1656	Asymmetric C=C

The authors are grateful to the D.S.I.R. for a maintenance grant to one of them (A. F. T.) and to Sir John Simonsen, F.R.S., and Dr. R. A. E. Galley, Directors of Colonial Products Research, for kindly arranging the collection of seeds of *Picralima nitida* in W. Africa.

The Dyson Perrins Laboratory, Oxford University. [*Received, May 25th*, 1954.]

Branched-chain Thia-alkanebis(quaternary Ammonium) Salts as Ganglion-blocking Agents.

By K. J. M. Andrews, F. Bergel, and A. L. Morrison.

[Reprint Order No. 5416.]

Thia-alkanebisammonium compounds have been synthesised with chain lengths approximating to five and six carbon atoms and having one or two methyl groups attached to the chain.

In a previous paper (*J.*, 1953, 2998), thia- and dithia-alkanebis(trialkylammonium) salts were described which showed ganglion-blocking activity. These were straight-chain compounds analogous to " Hexamethonium," with sulphur replacing a methylene group. As these sulphides could be considered as derivatives of choline, it was decided to investigate the effect on pharmacological activity of replacement of the choline by a methylcholine group. A few of these branched chain thia- and dithia-compounds have, therefore, been prepared with a methyl group in the α- or β-position to one of the nitrogen atoms. An appreciable increase in activity, as measured on the blood pressure of the cat and blocking of transmission in the cat superior cervical sympathetic ganglion, was caused by the introduction of a methyl group in the β-position. 2-Methyl-3-thiapentane-1 : 5-bis(trimethylammonium iodide) (Ro 3-0484) was found to be about twice as potent as " Hexamethonium " and slightly longer lasting (unpublished work by Drs. B. Pellmont, H. Bächtold, and L. O. Randall).

The thia-compounds were prepared by standard methods, *i.e.*, by reaction of the chloro-compound with a sodium mercaptide or sodium sulphide. The dithia-compound was prepared by oxidation of the thiol with iodine. However, when 1-chloro-2-dimethylaminopropane (Schultz and Sprague, *J. Amer. Chem. Soc.*, 1948, **70**, 48), freshly liberated at 0° from the hydrochloride (the identity of which was shown by the melting point and the melting point of its picrate), was treated with 2-mercaptoethyldimethylamine, the expected product was not obtained; the only material isolated, after quaternisation of the product with methyl iodide, was the known 2-methyl-3-thiapentane-1 : 5-bis(trimethylammonium iodide) :

$$Me_2N{\cdot}CHMe{\cdot}CH_2Cl + NaS{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2 \longrightarrow Me_2N{\cdot}CH_2{\cdot}CHMe{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2$$

A similar rearrangement occurred when sodium sulphide was used in the place of the mercaptide.

The ease with which 1-chloro-2-dimethylaminopropane isomerises has been demonstrated by Schultz and Sprague (*loc. cit.*) and by Ofner (*J.*, 1951, 1800) in connection with the synthesis of Amidone.

In order to synthesise the required 2 : 5-bisdimethylamino-3-thiahexane, the known 1-dimethylamino-5-hydroxy-3-thiahexane (Laskowski and Clinton, *J. Amer. Chem. Soc.*, 1947, **69**, 519) was converted into the chloride which was condensed with dimethylamine. The non-identity of the product with the compound prepared by the previous synthesis supported the view that the 1-chloro-2-dimethylaminopropane isomerised rapidly in the presence of the sodium mercaptide and reacted largely as 2-chloropropyldimethylamine.

The tertiary bisdimethylamino-compounds obtained by these reactions were quaternised with methyl and ethyl iodide.

Experimental

1 : 5-*Bisdimethylamino-2-methyl-3-thiapentane*.—To sodium (1·5 g.), dissolved in ethanol (50 ml.), was added 2-mercaptoethyldimethylamine (6·9 g.) in ethanol (8 ml.) in a nitrogen atmosphere. A solution of 2-chloropropyldimethylamine (8 g.) (Washington, Office of Publication Board, Dept. Commerce Report P.B. 981, p. 96) in ethanol (25 ml.) was then added dropwise. The mixture was heated under reflux for 1 hr. and then set aside for 15 hr. The precipitated sodium chloride was filtered off and the filtrate evaporated *in vacuo*. The residual *base* was

distilled, having b. p. 63°/0·2 mm., n_D^{18} 1·4783 (yield 84%) (Found: N, 15·0; S, 16·5. $C_9H_{22}N_2S$ requires N, 14·8; S, 16·9%).

This base (1·9 g.), in benzene (10 ml.), was cooled in ice, and a cold solution of methyl iodide (2·9 g.) in benzene (5 ml.) was added. The semi-solid mixture was set aside for 24 hr., after which it was diluted with ether and filtered, and the solid was washed with ether and dried. Recrystallisation from ethanol gave colourless *2-methyl-3-thiapentane*-1 : 5-*bis*(*trimethylammonium iodide*), m. p. 250° (decomp.) (3·8 g., 81%). After a further recrystallisation the m. p. was 254° (decomp.) (Found: N, 6·0; S, 6·8. $C_{11}H_{28}N_2SI_2$ requires N, 5·9; S, 6·8%).

The corresponding *diethiodide* was prepared from the base (2 g.) and ethyl iodide (3·4 g.) in ethanol (10 ml.) at 75° (5 hr.) and then room temp. (2 days). After two recrystallisations from ethanol–methanol the m. p. was 248—249° (decomp.) (Found: C, 31·7; H, 6·6; N, 5·4. $C_{13}H_{32}N_2SI_2$ requires C, 31·1; H, 6·4; N, 5·6%).

2-Methyl-3-thiahexane-1 : 6-*bis*(*trimethylammonium Iodide*).—Sodium (1 g.) was dissolved in dry ethanol (30 ml.) in a nitrogen atmosphere, and 3-mercaptopropyldimethylamine (4·5 g.) in ethanol (5 ml.) was added. 2-Chloropropyldimethylamine in ethanol (15 ml.) was added dropwise, with occasional shaking, and the mixture was heated under reflux on a water-bath for 1 hr. After a further 30 min., the salt which had been precipitated was filtered off. The filtrate was evaporated and the residue was distilled *in vacuo*. The fraction, b. p. 67—69°/0·4 mm., n_D^{21} 1·4755, was collected (4·3 g., 56%). Quaternisation with methyl iodide in ether gave the *methiodide* (97%), which after two recrystallisations from ethanol–methanol had m. p. 199—200° (4·25 g., 89%) (Found: C, 29·5; H, 6·5; N, 5·1; S, 6·9. $C_{12}H_{30}N_2SI_2$ requires C, 29·5; H, 6·2; N, 5·7; S, 6·6%).

The corresponding diethiodide (prep.: 5 hr. at the b. p., overnight at room temp.), when crystallised from ethanol had m. p. 200—201° (7·3 g., 51%) (Found: C, 32·5; H, 7·0; N, 5·0. $C_{14}H_{34}N_2SI_2$ requires C, 32·6; H, 6·6; N, 5·4%).

1 : 5-*Bisdimethylamino*-2 : 4-*dimethyl*-3-*thiapentane* (Method according to Gilman *et al.*, *J. Amer. Chem. Soc.*, 1945, **67**, 1846).—Hydrated sodium sulphide ($Na_2S,9H_2O$) (30 g.) was heated at 120°, dissolving in its water of crystallisation. Hydrogen sulphide was then bubbled through the solution for several hours, until it was saturated. Nitrogen was substituted for the hydrogen sulphide, and 2-chloropropyldimethylamine (13·1 g.), freshly liberated from its hydrochloride, was added dropwise with stirring. The stirred solution was heated under reflux for 1 hr., cooled in ice, and extracted 3 times with ether. The ethereal extract was dried (Na_2SO_4), the ether evaporated, and the residual oil distilled. 2-Mercaptopropyldimethylamine distilled first, b. p. 50°/22 mm. (3·65 g.), and then 1 : 5-*bisdimethylamino*-2 : 4-*dimethyl*-3-*thiapentane*, b. p. 72—74°/0·6 mm., n_D^{22} 1·4786 (3·5 g.) (Found: N, 13·3; S, 15·6. $C_{10}H_{24}N_2S$ requires N, 13·7; S, 15·7%).

The *dimethiodide*, prepared in benzene at 0°, formed plates, m. p. 230° (decomp.), from methanol–ethanol (Found: C, 29·2; H, 6·0; N, 5·7; S, 7·1. $C_{12}H_{30}N_2SI_2$ requires C, 29·5; H, 6·2; N, 5·7; S, 6·6%).

2 : 5-*Dimethyl*-3 : 4-*dithiahexane*-1 : 6-*bis*(*trimethylammonium Iodide*) (cf. Renshaw *et al.*, *ibid.*, 1938, **60**, 1765).—Iodine (4·2 g.) dissolved in aqueous potassium iodide (12 g. in 60 ml.) was added, with water cooling, to 2-mercaptopropyldimethylamine (3·6 g.) dissolved in 5N-sodium hydroxide (6 ml.). The colourless mixture was made alkaline with sodium hydroxide solution and extracted 4 times with ether. The ethereal solution was dried (Na_2SO_4) and, after filtration, the ether was evaporated to give an oil (3·1 g.). This was dissolved in dry ether (10 ml.) and cooled in ice. Methyl iodide (4·1 g.), in dry ether (10 ml.), was added and the mixture was allowed to warm to room temperature. The solid quaternary salt which had separated was collected by filtration and dried. After two (or more) recrystallisations from ethanol–methanol, it had m. p. 223° (decomp.) (2·45 g.) (Found: C, 27·3; H, 5·8; N, 5·5. Calc. for $C_{12}H_{30}N_2S_2I_2$ (C, 27·7; H, 5·8; N, 5·4%). Renshaw *et al.* (*loc. cit.*) give m. p. 207—208° (decomp.).

Attempted Preparation of 3-*Thiahexane*-1 : 5-*bis*(*trimethylammonium Iodide*).—1-Chloro-2-dimethylaminopropane was liberated from the hydrochloride (13 g.), m. p. 102—104° (Schultz and Sprague, *J. Amer. Chem. Soc.*, 1948, **70**, 48), at 0° with 30% sodium hydroxide solution. The oil was separated and the aqueous layer was extracted twice with ether. The oil and the ethereal solution were combined and set aside in the refrigerator while drying (KOH). After filtration, the ether was evaporated *in vacuo* at room temperature. 1-Chloro-2-dimethylaminopropane (8 g.) remained as an oil.

Sodium (1·55 g.) was dissolved in ethanol (48 ml.), and 2-mercaptoethyldimethylamine (7·1 g.) in dry ethanol (8 ml.) was added in a nitrogen atmosphere. Then the chloro-amine (8 g.) in

ethanol (20 ml.) was added dropwise with shaking. Sodium chloride was precipitated immediately. The mixture was heated under reflux for ½ hr. and, after cooling, filtered, and the filtrate was evaporated *in vacuo*. The residual oil was distilled, having b. p. 69°/0·05 mm., n_D^{20} 1·4768 (8·2 g., 66%) (Found: N, 15·0; S, 16·5. Calc. for $C_9H_{22}N_2S$: N, 14·7; S, 16·8%). Its picrate had m. p. 137—140°, not depressed in admixture with the picrate of 1 : 5-bisdimethylamino-2-methyl-3-thiapentane. The methiodide, prepared in benzene, after two recrystallisations from methanol had m. p. 253—254° (decomp.), undepressed in admixture with 2-methyl-3-thiapentane-1 : 5-bis(trimethylammonium iodide), m. p. 254° (decomp.) (Found: C, 28·0; H, 6·0; N, 5·2. Calc. for $C_{11}H_{28}N_2SI_2$: C, 27·9; H, 6·0; N, 5·9%). The picrates derived from these two samples of methiodide had the same m. p. (231°) and there was no depression of the m. p. when they were mixed.

5-Chloro-1-dimethylamino-3-thiahexane Hydrochloride.—Thionyl chloride (9·5 ml.) in dry chloroform (25 ml.) was added during 1½ hr. to a stirred solution of 1-dimethylamino-5-hydroxy-3-thiahexane (20 g.) (Laskowski and Clinton, *loc. cit.*) in dry chloroform (60 ml.) at −30°. The solution was then stirred for 1 hr. at room temperature, heated under reflux for a further hour, and allowed to cool before addition of dry ether (300 ml.). The flocculent precipitate of needles was collected and recrystallised from ethanol–ethyl acetate by addition of ether; this *salt* had m. p. 95·5° (19 g., 71%) (Found: N, 5·9; S, 14·5. $C_7H_{17}NSCl_2$ requires N, 6·4; S, 14·7%). The free base, liberated from the hydrochloride, had b. p. 50—51°/0·18 mm., n_D^{22} 1·4875.

1 : 5-Bisdimethylamino-3-thiahexane.—5-Chloro-1-dimethylamino-3-thiahexane (8 g.), freshly liberated from the hydrochloride, 5N-sodium hydroxide (9 ml.), and 28% w/v aqueous dimethylamine (9 ml.) were mixed and shaken for 16 hr. The oily layer was separated and the aqueous layer was extracted with ether. When the ethereal extract and the oil were combined, part of the oil remained undissolved and was washed out with water. The ethereal solution was dried (Na_2SO_4) and evaporated and the residual *base* distilled (b. p. 40—2°/0·1 mm., $n_D^{21\cdot5}$ 1·4735; 3·6 g., 43%) (Found: N, 15·1; S, 17·1. $C_9H_{22}N_2S$ requires N, 14·7; S, 16·8%). The picrate, prepared in alcohol, had m. p. 125°.

Reaction with methyl iodide in ether at 0° was rapid. After 3 days at room temp. the *dimethiodide* was filtered off. Recrystallised twice from methanol, it had m. p. 238—240° (decomp.) (47%) (Found: C, 27·6; H, 5·9; N, 5·8. $C_{11}H_{28}N_2SI_2$ requires C, 27·9; H, 6·0; N, 5·9%). The picrate had m. p. 211—211·5°.

The *diethiodide*, prepared in boiling ethanol (5 hr.) and recrystallised twice from ethanol, had m. p. 203—204° (47%) (Found: C, 30·7; H, 6·4; N, 5·3. $C_{13}H_{32}N_2SI_2$ requires C, 31·1; H, 6·4; N, 5·6%).

Attempted Preparation of 1 : 5-Dimethyl-3-thiapentane-1 : 5-bis(trimethylammonium Iodide).—By the method given for the preparation of 1 : 5-bisdimethylamino-2 : 4-dimethyl-3-thiapentane, but by treating the sodium sulphide with 1-chloro-2-dimethylaminopropane (16·6 g.), an oil was obtained which, on distillation, gave a thiol (1·5 g.), b. p. 46°/12 mm., and also an oil (6·2 g.), b. p. 59—63°/0·2 mm., $n_D^{20\cdot5}$ 1·4786. The methiodide, prepared from the latter in benzene in good yield and recrystallised from methanol–ethanol, had m. p. 230—231° (decomp.), and there was no depression in admixture with the 2 : 4-dimethyl compound of m. p. 229—230° (decomp.). Also, the picrate from the methiodide had m. p. 213—215° (decomp.) and there was no depression of this m. p. in admixture with the picrate of the 2 : 4-dimethyl compound of m. p. 212—214° (decomp.).

We acknowledge technical assistance by Messrs. W. C. Spurden and A. J. Westoby.

RESEARCH DEPARTMENT, ROCHE PRODUCTS LIMITED,
WELWYN GARDEN CITY, HERTS.

[*Received, May 27th,* 1954.]

Ring Expansion. Part I. The Dienone–Phenol Rearrangement of spiro[5 : 5]*Undeca*-1 : 4-*diene*-3-*one.*

By R. H. Burnell and W. I. Taylor.

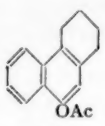
[Reprint Order No. 5444.]

A convenient synthesis of *spiro*[5 : 5]undecan-3-one from *cyclo*hexanone and vinyl cyanide is given. The spiran was converted into the dienone, which readily rearranged in acetic anhydride–sulphuric acid with simultaneous ring expansion, yielding 2′-acetoxybenzo*cyclo*heptene.

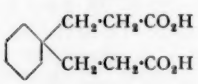
Arnold, Buckley, and Dodson (*J. Amer. Chem. Soc.*, 1950, **72**, 3153) have shown that the unsaturated *spiro*-ketone (I) rearranges in acid, with ring expansion, to the phenanthrene derivative (II). We wished to learn whether a six-membered ring could be expanded similarly in good yield to form a seven-membered ring; for this purpose *spiro*[5 : 5]undecan-3-one appeared to be a suitable starting material.

Bruson and Riener (*ibid.*, 1942, **64**, 2850) found that the addition of vinyl cyanide to *cyclo*hexanone in the presence of Triton B afforded, along with mono- and tetrakis-cyanoethyl derivatives of *cyclo*hexanone, 9% of 2 : 2-bis-2′-cyanoethyl*cyclo*hexanone. We have raised this yield to a reproducible 18—20% by addition of only a limited quantity of vinyl cyanide. Recently, in a work available to us only in abstract, Levina, Shusherina, and Kaminskaya (*Doklady Akad. Nauk S.S.S.R.*, 1952, **86**, 79; *Chem. Abs.*, 1953, **47**, 4849) reported a 40% yield of the biscyanoethyl ketone by the use of 1% of dry sodium hydroxide as catalyst : we have been unable to duplicate their results and have consistently obtained intractable polymers.

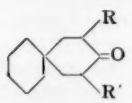
(I)



(II)



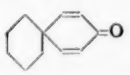
(III)

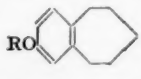


(IV)

Alkaline hydrolysis of 2 : 2-bis-2′-cyanoethyl*cyclo*hexanone followed by Wolff-Kishner reduction afforded the acid (III), which on esterification and Dieckmann ring closure gave ethyl 3-oxo*spiro*[5 : 5]undecane-2-carboxylate (IV; R = H, R′ = CO_2Et). Hydrolysis then furnished the *spiro*-ketone (IV; R = R′ = H). Bromination of the ketone in acetic acid containing hydrobromic acid resulted in a dibromo-derivative which must be *cis*-2 : 4-dibromo*spiro*[5 : 5]undecan-3-one (IV; R = R′ = Br) since the carbonyl absorption is at the position (1756 cm.$^{-1}$) expected (Corey, *J. Amer. Chem. Soc.*, 1954, **76**, 175) for a carbonyl group in a *cyclo*hexane ring sterically hindered by two equatorially substituted bromine atoms. Elimination of hydrogen bromide by boiling collidine yielded low-melting dienone (V) which was purified by chromatography. This rearranged smoothly at room temperature in acetic anhydride containing a drop of sulphuric acid, to yield the acetate (VI; R = Ac) which was readily hydrolysed to 2′-hydroxybenzo*cyclo*heptene identical with an authentic sample kindly provided by Professor V. Prelog.

(V)





(VI)

Refluxing the dibromo-ketone (IV; R = R′ = Br) with 2 : 4-dinitrophenylhydrazine in acetic acid for ten minutes under nitrogen afforded the 2 : 4-dinitrophenylhydrazones of 4-bromo*spiro*[5 : 5]undec-1-en-3-one and the dienone (V). The former derivative was smoothly converted into the latter after a further fifteen minutes' refluxing under the same conditions.

Experimental

2 : 2-*Bis*-2′-*cyanoethyl*cyclo*hexanone*.—Vinyl cyanide (90 g.) was added during 80 min. to a vigorously stirred solution of Triton B (10 g.) in *cyclo*hexanone (180 g.) at 30—35°. The mixture was acidified, filtered, washed several times with water, and distilled, giving fractions: (i) *cyclo*hexanone; (ii) b. p. 150—190°/1 mm. (21 g.), largely 2-2′-cyanoethyl*cyclo*hexanone; (iii) b. p. 214—216°/1 mm., crystallised from benzene–light petroleum to furnish **2 : 2-bis-2′-cyano**ethyl*cyclo*hexanone (61 g.), m. p. 63° (Found: C, 70·9; H, 7·7. Calc. for $C_{12}H_{16}ON_2$: C, 70·5; H, 7·9%) [*semicarbazone*, m. p. 196° (from ethanol) (Found: N, 26·5. $C_{13}H_{19}ON_5$ requires N, 24·0%)].

cyclo*Hexanone*-**2 : 2-*bis*-β-*propionic Acid*.**—Hydrolysis of the dicyanide (15 g.) with boiling aqueous potassium hydroxide afforded the diacid, m. p. 136° (lit., 141°) (16 g.) (Found: C, 59·4; H, 7·6. Calc. for $C_{12}H_{18}O_5$: C, 59·6; H, 7·5%).

cyclo*Hexane*-**1 : 1-*bis*-β-*propionic Acid*.**—The foregoing acid (49 g.), potassium hydroxide (20 g.), and 85% hydrazine (23 c.c.) were refluxed for 8 hr. in ethylene glycol (250 c.c.), then the condenser was removed and the temperature allowed to rise to 200° by distillation of all the water. After 3·5 hr. at 200° the solution was cooled, acidified, and extracted with ether to yield crude *cyclo*hexane-1 : 1-bis-β-propionic acid (39 g.), which was esterified without purification to the *diethyl* ester (44 g.), b. p. 207—208°/19 mm. (Found: C, 67·5; H, 9·9; OEt, 15·8. $C_{16}H_{28}O_4$ requires C, 67·6; H, 9·9; 2OEt, 15·9%).

Ethyl **3-*oxo*spiro[5 : 5]*undecane*-2-*carboxylate*.**—The ester (9·7 g.) was added slowly to a rapidly stirred suspension of sodium (0·77 g.) in toluene (30 c.c.) at 110—115°. After 5 hr. the solution was cooled in ice, then added to cold 10% aqueous acetic acid. The toluene layer was separated, washed successively with water, aqueous sodium carbonate, and water, dried (Na_2SO_4), and distilled to furnish *ethyl* **3-*oxo*spiro[5 : 5]*undecane*-2-*carboxylate*** (4·0 g., 51%), b. p. 160°/20 mm. (Found: C, 70·6; H, 9·3. $C_{14}H_{22}O_3$ requires C, 70·6; H, 9·3%). The ultra-violet absorption spectrum, in ethanol, showed a maximum at 256 mμ (log ε 3·95).

spiro[5 : 5]*Undecan*-**3-*one*.**—The *spiro*-keto-ester (1·5 g.), when refluxed for 12 hr. in 50% aqueous ethanol (10 c.c.) containing concentrated hydrochloric acid (2 c.c.), yielded the ***spiro*-ketone** (0·73 g.), b. p. 135—140°/14 mm., characterised as its **2 : 4-*dinitrophenylhydrazone***, m. p. 121° (Found: C, 58·9; H, 6·5; N, 16·2. $C_{17}H_{22}O_4N_4$ requires C, 59·0; H, 6·4; N, 16·2%).

cis-**2 : 4-*Dibromo*spiro[5 : 5]*undecan*-3-*one*.**—The *spiro*-ketone (0·7 g.) in acetic acid (3 c.c.) decolorised bromine (1·36 g.) in acetic acid (3 c.c.) instantly, and after the addition of hydrobromic acid (1 c.c.) the whole was kept overnight. Dilution with water, followed by extraction with ether, furnished the cis-***dibromo*-spiro-*ketone*** (1·3 g., 93%), m. p. 132° (from ether) (Found C, 40·8; H, 5·0. $C_{11}H_{16}OBr_2$ requires C, 40·8; H, 5·0%).

spiro[5 : 5]*Undeca*-**1 : 4-*dien*-3-*one*.**—The dibromo-*spiro*-ketone (1·3 g.) and collidine (3 c.c.) were gently boiled for 4 min., then cooled, and the collidine hydrobromide was filtered off. The filtrate was taken up in ether, washed twice with 5% hydrochloric acid, dried (Na_2SO_4), and concentrated. The crude product (0·8 g.) after chromatography over activated alumina afforded the *spiro*-dienone (250 mg.), m. p. 82°, with a maximum in the ultra-violet at 235 mμ (log ε 4·2). Its **2 : 4-*dinitrophenylhydrazone***, crystallised from ethanol–chloroform, had m. p. 163—164° (Found: C, 59·2; H, 5·2. $C_{17}H_{18}O_4N_4$ requires C, 59·6; H, 5·3%) and showed maxima in the ultra-violet at 257 and 395 mμ (log ε 4·15 and 4·44 respectively).

2′-*Hydroxybenzo*cyclo*heptene*.**—One drop of concentrated sulphuric acid in acetic anhydride (2 c.c.) was added to the *spiro*-dienone (0·15 g.) in acetic anhydride (7 c.c.). After 7 hr. water (25 c.c.) was added and the solution was set aside at 0° for 12 hr. The precipitated **2-*acetoxy*-*benzo*cyclo*heptene*** (90 mg.) had m. p. 61—62° after crystallisation from ethanol (Found: C, 76·3; H, 8·1. $C_{15}H_{16}O_2$ requires C, 76·4; H, 7·9%). Mild alkaline hydrolysis of the acetate furnished 2′-hydroxybenzo*cyclo*heptene, m. p. 72° [from light petroleum (b. p. 60—80°)] (Found: C, 81·8; H, 8·8. Calc. for $C_{11}H_{14}O$: C, 81·5; H, 8·7%). The phenol and its acetate gave undepressed mixed m. p.s with authentic specimens (Prelog, Ruzicka, and Metzler, *Helv. Chim. Acta*, 1947, **30**, 1883).

4-*Bromo*spiro[5 : 5]*undec*-1-*en*-3-*one*.—The dibromo-*spiro*-ketone (130 mg.) in acetic acid (5 c.c.) was added to a hot solution of **2 : 4-dinitrophenylhydrazine** (80 mg.) in acetic acid (3 c.c.), then heated for 10 min. in nitrogen. On cooling, the orange **2 : 4-*dinitrophenylhydrazone*** (65 mg.) of 4-bromo*spiro*[5 : 5]undec-1-en-3-one separated (m. p. 157°), which was crystallised from chloroform–ethanol for analysis (Found: C, 48·3; H, 4·6; N, 13·3. $C_{17}H_{19}O_4N_4Br$ requires C, 48·2; H, 4·5; N, 13·2%). The ultra-violet absorption spectrum showed max. at 256 and 375 mμ (log ε 4·1 and 4·4 respectively). Concentration of the acetic acid mother-liquors and

addition of two drops of water furnished *spiro*[5 : 5]undeca-1 : 4-dien-3-one 2 : 4-dinitrophenylhydrazone (43 mg.), m. p. 163—164°, undepressed in m. p. by the sample prepared as above.

We are indebted to the National Research Council of Canada for a grant and to Mr. W. Fulmor and his staff of American Cyanamid Company, Lederle Laboratories Division, for the infra-red spectra.

THE CHEMICAL LABORATORIES,
THE UNIVERSITY OF NEW BRUNSWICK. [*Received, June 4th*, 1954.]

Tertiary Alkoxides of Thorium.

By D. C. BRADLEY, M. A. SAAD, and W. WARDLAW.

[Reprint Order No. 5386.]

The thorium alkoxides, $Th(OR)_4$ (R = CMe_3, CMe_2Et, $CMeEt_2$, CEt_3, CMe_2Pr^n, CMe_2Pr^i, $CMeEtPr^n$, and $CMeEtPr^i$) were prepared from $Th(OPr^i)_4$ by alcohol interchange. The molecular weights in benzene (ebullioscopic method) and boiling points under reduced pressure were determined. The results are discussed in terms of the stereochemical theory advanced to account for the properties of the alkoxides of other Group IVA elements.

THE new alkoxides of thorium, $Th(OR)_4$ (R = Me, Et, or Pr^i), which we recently (*J.*, 1954, 1091) prepared were complex non-volatile solids whose alkaline reaction suggested the presence of considerable ionic character. In view of the stereochemical theory developed to explain the remarkable physicochemical properties of the alkoxides of titanium, zirconium, and hafnium (Bradley, Mehrotra, and Wardlaw, *J.*, 1952, 2027, 4204, 5020; 1953, 1634, 2025) it was considered desirable to investigate the tertiary alkoxides of thorium also.

Eight new alkoxides $Th(OR)_4$ (see Table 1) were prepared by alcohol interchange involving thorium tetra*iso*propoxide and the appropriate alcohol :

$$Th(OPr^i)_4 + 4ROH \longrightarrow Th(OR)_4 + 4Pr^iOH$$

Molecular weights were determined ebullioscopically in benzene and, where possible, boiling points were measured under reduced pressure. The data, including the calculated molecular complexities ($x = M$/formula weight), are recorded in Table 1.

TABLE 1.

R in $Th(OR)_4$	B. p./mm.	*M*	*x*
CMe_3	160°/0·1 (subl.)	1787	3·4
CMe_2Et	208°/0·3	1601	2·8
$CMeEt_2$	148°/0·1	1156	1·8
CMe_2Pr^n	Decomp. >120°/0·1	1653	2·6
CMe_2Pr^i	"	1444	2·3
CEt_3	148°/0·05	714	1·0
$CMeEtPr^n$	153°/0·1	1171	1·7
$CMeEtPr^i$	139°/0·05	709	1·0

The thorium derivative of ethylmethyl*iso*propylcarbinol (1-ethyl-1 : 2-dimethylpropanol) appears to be the most volatile organic compound of thorium yet recorded and several of the other compounds listed in Table 1 are more volatile than the thorium–tetraacetylacetone complex, the only other volatilisable organic thorium compound hitherto reported.

It is evident in Table 1 that the volatility and molecular complexity of thorium alkoxides are determined by the size and shape of the alkyl group. There can be little doubt that this behaviour is predominantly the result of stereochemical effects. Thus there will be only minor variations in electronic effect from one alkyl group to another because they are all tertiary alkyls. Moreover, the molecular complexities decrease with increase in size of the alkyl group and this behaviour is consistent with the stereochemical theory previously advanced to account for the behaviour of the alkoxides of silicon, titanium,

zirconium, and hafnium. This theory suggests that intermolecular bonding M···O involving the central atom M (= Ti, Zr, or Hf) and oxygen from a neighbouring alkoxide group gives rise to complex non-volatile alkoxides. In the monomeric alkoxides the central atom is shielded by the rotation of the branched alkoxide groups, intermolecular attraction is minimised, and the compounds are relatively volatile. The theory was supported by a comparison of the behaviour of the alkoxides of silicon, titanium, zirconium, and hafnium. This showed that the size of the central atom controlled the effectiveness of an alkoxide group in shielding. Thus the effect of chain branching on volatility was much greater in the case of zirconium (or hafnium) than in titanium and least for silicon. Thorium, whose atomic radius is the largest of the Group IVA elements, gives alkoxides with properties which accord with these stereochemical requirements. The contrast in the properties of thorium, zirconium, titanium, and silicon alkoxides is demonstrated in Table 2, which contains the boiling points (°C at 0·1 mm.) and molecular complexities (in parentheses) of selected compounds having an increasing degree of chain branching of the alkyl group.

TABLE 2.

	Si	Ti	Zr	Th
Atomic radius, Å	1·17	1·36	1·48	1·65
Alkoxide				
O·CH_2Me	−15° * (1·0)	102° (2·4)	180° (3·4)	Non-volatile
O·$CHMe_2$	15 (1·0)	49 (1·4)	160 (3·0)	210° ((3·8)
O·CMe_3	—	52 (1·0)	50 (1·0)	160 (3·4)
O·$CMeEt_2$	—	128 (1·0)	128 (1·0)	148 (1·8)
O·CEt_3	—	166 (1·0)	166 (1·0)	154 (1·0)

* Calculated.

An interesting feature of Table 2 is the behaviour of the monomeric tertiary C_7-alkoxides of titanium, zirconium, and thorium. Their boiling points are close together, suggesting that they have similar molar heats of vaporisation because the effect of the central atom has been obviated by the screen of organic groups. This emphasises the powerful effect of highly branched alkoxide groups in shielding a central atom. Thus, in addition to suppressing the intermolecular attraction involving the central atom and oxygen, it appears that the contribution due to the marked ionic character in the thorium alkoxide is also nullified.

EXPERIMENTAL

The special precautions to avoid hydrolysis reported earlier (*J.*, 1954, 1091) were observed and, owing to the sensitivity of thorium tertiary alkoxides to oxygen, experiments were conducted in the presence of oxygen-free nitrogen. Otherwise the apparatus and experimental technique used were similar to those described by Bradley, Mehrotra, and Wardlaw (*loc. cit.*);

TABLE 3.

R	$Th(OPr^i)_4$ taken (g.)	ROH taken (g.)	C_6H_6 (ml.)	Yield of $Th(OR)_4$ (g.)	Th (%) Found	Th (%) Reqd.
CMe_3	5·22	*ca.* 150 *	*ca.* 350 *	5·6 [a]	45·15	44·25
CMe_2Et	8·4	10·8	70	10·3 [b]	40·85	40·0
$CMeEt_2$	7·6	8·44	57·4	10·4 [a]	36·7	36·4
CMe_2Pr^n	6·7	10·22	56	8·14 [c]	36·95	,,
CMe_2Pr^i	4·07	6·12	55	5·04 [c]	37·15	,,
CEt_3	4·0	8·29	60	5·63 [d]	33·7	33·5
$CMeEtPr^n$	4·7	6·5	60	7·0 [c]	34·1	,,
$CMeEtPr^i$	6·9	8·0	60	10·4 [c]	33·0	,,

* Added in 3 stages.
[a] White solid. [b] Viscous liquid. [c] Very viscous liquid. [d] Mobile liquid.

TABLE 4.

R in $Th(OR)_4$	Solute, range of wts. (g.)	Benzene (g.)	R in $Th(OR)_4$	Solute, range of wts. (g.)	Benzene (g.)
CMe_3	0·120—1·159	15·72	CMe_2Pr^i	0·168—1·135	17·28
CMe_2Et	0·170—1·942	16·30	CEt_3	0·219—1·324	16·21
$CMeEt_2$	0·112—0·993	16·71	$CMeEtPr^n$	0·219—0·795	14·82
CMe_2Pr^n	0·282—1·201	17·84	$CMeEtPr^i$	0·138—0·922	14·20

accordingly the experimental details are presented only in Table 3. The molecular-weight determinations are given in Tables 1 and 4. No evidence of variation of molecular complexity with concentration of solute was observed within the ranges of concentration reported.

One of us (M. A. S.) thanks Alexandria University for study leave.

BIRKBECK COLLEGE, MALET STREET, W.C.1. [*Received, May 14th,* 1954.]

---

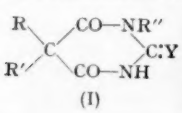
cyclo*Octatetraene Derivatives. Part VI.* Preparation of Barbituric Acids.*

By W. O. JONES and D. S. WITHEY.

[Reprint Order No. 5409.]

Some barbituric and thiobarbituric acids containing a *cyclo*octyl or a *cyclo*oct-2-enyl group in the 5-position have been prepared and their narcotic actions examined.

SOME barbiturates and thiobarbiturates possessing a *cyclo*alkyl or a *cyclo*alkenyl group in the 5-position have high narcotic activity. Representatives carrying a five-membered (Pentenal) (I; $R = C_5H_7$, $R' = C_2H_5$, $R'' = H$, $Y = O$) or a six-membered ring (*e.g.*, Thialbarbitone) (I; $R = C_6H_9$, $R' = C_3H_5$, $R'' = H$, $Y = S$) have been used in pharmacy, and it was therefore of interest to prepare and examine analogous barbituric acid derivatives containing an eight-membered ring.



(I)

A high yield (85%) of *cyclo*octylmalonic ester obtained from ethyl malonate and *cyclo*octyl bromide was unexpected because of the usual tendency of *cyclo*alkyl halides to lose hydrogen halide in alkali: in analogous reactions with *cyclo*pentyl iodide and *cyclo*hexyl bromide, the highest recorded yields of *cyclo*alkylmalonic esters are 50% (Verwey, *Ber.*, 1896, **29**, 1996) and 44% (Hiers and Adams, *J. Amer. Chem. Soc.*, 1926, **48**, 2385) respectively. In the preparation of *cyclo*octylmalonic acid (m. p. 124°) by alkaline hydrolysis it was essential to make the product strongly acid, for at pH 5—6 the crystals (m. p. 176°) which separated proved to be potassium trihydrogen bis*cyclo*octylmalonate,

$$[C_8H_{15}\cdot CH(CO_2H)_2, C_8H_{15}\cdot CH(CO_2H)(CO_2K)]$$

Malonic acid itself forms a similar salt.

Attempts to methylate *cyclo*octylmalonic ester gave extremely low yields (about 4%), and provide another example of the difficulty of introducing a second alkyl group into a monosubstituted malonic ester (cf. Dox and Yoder, *ibid.*, 1922, **44**, 1566; Schoule, Keltch, and Suranson, *ibid.*, 1930, **52**, 2440), particularly when the larger of the two groups has been introduced first. It has recently been claimed (B.P. 649,682/1951) that the difficulty can be overcome by a modified procedure but it was not successful when applied to dibutyl *cyclo*octylmalonate. The required *cyclo*octylmethylmalonic ester was ultimately obtained in 55% yield by inverting the order of alkylation.

*cyclo*Octen-2-ylmalonic ester was prepared by treating sodiomalonic ester with 3-bromo*cyclo*octene or 1 : 2-dibromo*cyclo*octane (cf. Mousseron, Manon, and Combes, *Bull. Soc. chim.*, 1949, 396), identity of the products being confirmed by hydrolysis to *cyclo*oct-2-enylmalonic acid. 1-Bromo*cyclo*octene did not react with sodiomalonic ester.

Several barbituric and thiobarbituric acids containing a *cyclo*octyl or a *cyclo*oct-2-enyl group have been prepared by standard methods. The products containing a 5-allyl group were prepared by direct allylation of the 5-monosubstituted barbituric acid (cf. Volwiler, *J. Amer. Chem. Soc.*, 1925, **47**, 2236) and not through the corresponding allylmalonic ester, but an attempt to introduce a methyl group into the 5-position of 5-*cyclo*octylbarbituric acid failed.

Sodium salts of the 5 : 5-disubstituted barbituric and thiobarbituric acids were all less toxic than Hexobarbitone, but the therapeutic ratio was usually much lower, the best

* Part V, *J.*, 1954, 1808.

product being 5-methyl-5-*cyclo*octylbarbituric acid with a therapeutic ratio about equal to that of Hexobarbitone (I; $R = C_6H_9$, $R' = R'' = CH_3$, $Y = O$).

It is known that two substituents (preferably having together 6—8 carbon atoms) on the 5-position of barbituric acids appear to be essential for narcotic action (Dox and Yoder, *loc. cit.*, p. 1141). To test the possibility that one bulky eight-carbon substituent would have the same effect, 5-*cyclo*oct-2′-enylbarbituric acid was also examined, but it was devoid of narcotic action.

Experimental

Diethyl cyclo*Octylmalonate.*—Ethyl malonate (185 g.) was added to a solution of sodium ethoxide (26·5 g. of sodium in 600 ml. of absolute ethanol), and most of the ethanol (410 ml.) was distilled off. *cyclo*Octyl bromide (220 g.) was added to the pasty residue and heating continued (107° internal temp.) for 50 hr., most of the remaining ethanol (120 ml.) being allowed to distil away. The cooled mixture was treated with water, extracted with ether, and dried. On evaporation and fractionation, apart from a fraction (22 g.; *cyclo*octene), the whole product distilled at 132°/0·7 mm., having n_D^{24} 1·4628. The colourless oil obtained (198 g., 85%) was the required *ester* (Found: C, 66·7; H, 9·6. $C_{15}H_{26}O_4$ requires C, 66·7; H, 9·6%). Hydrolysis with alcoholic potassium hydroxide, followed by acidification with hydrochloric acid to Congo-red, yielded cyclo*octylmalonic acid*, plates (from water), m. p. 123—124° (decomp.) (Found: C, 61·3; H, 8·3%; equiv., 107·5. $C_{11}H_{18}O_4$ requires C, 61·7; H, 8·4%; equiv., 107). When the hydrolysis solution was acidified to pH 6 only, *potassium trihydrogen bis*cyclo*octylmalonate* separated in rhombs, m. p. 176—177° (decomp.) (Found: C, 56·7; H, 7·5%; equiv., 156. $C_{22}H_{35}O_8K$ requires C, 56·6; H, 7·5%; equiv., 155).

Di-n-*butyl* cyclo*Octylmalonate* (cf. B.P. 649,682).—Di-*n*-butyl malonate (108 g.) and *cyclo*octyl bromide (115 g.) were stirred together at 100°, and a solution of sodium butoxide in butanol (from 12·65 g. of sodium and 228 g. of *n*-butanol) was added dropwise during 70 hr. Water was added to the cooled mixture and the oil was taken up in benzene, dried, and fractionated. The required *ester* (51 g., 31%) had b. p. 116°/0·15 mm., n_D^{25} 1·4641 (Found: C, 69·2; H, 10·4. $C_{19}H_{34}O_4$ requires C, 69·9; H, 10·4%).

*Diethyl Methyl*cyclo*octylmalonate.*—Ethyl sodiomethylmalonate (from 87 g. of ester) was heated for 60 hr. at 100—104° (internal) with *cyclo*octyl bromide (95 g.), and the product isolated in the normal manner. The disubstituted malonic *ester* (78 g., 55%) had b. p. 140—142°/2 mm., n_D^{20} 1·4652 (Found: C, 67·5; H, 9·8. $C_{16}H_{28}O_4$ requires C, 67·6; H, 9·9%). On hydrolysis it gave *methyl*cyclo*octylmalonic acid*, colourless plates (from water), m. p. 176° (decomp.) (Found: C, 63·3; H, 8·8. $C_{12}H_{20}O_4$ requires C, 63·2; H, 8·8%).

Attempts to Alkylate cyclo*Octylmalonic Esters.*—(*a*) Diethyl *cyclo*octylmalonate (13·5 g.) was heated with methyl iodide (8·0 g.) in the presence of sodium ethoxide in absolute ethanol until the mixture no longer gave an alkaline reaction with litmus paper (62 hr.). The resulting ester (11·8 g.), b. p. 107—109°/0·02—0·03 mm., n_D^{21} 1·4637, was mainly unchanged *cyclo*octylmalonic ester since the main product on hydrolysis was *cyclo*octylmalonic acid. A very small amount (4%) of methyl*cyclo*octylmalonic acid, m. p. and mixed m. p. 176° (decomp.), was also isolated.

(*b*) The method of achieving the reverse order of alkylation described in B.P. 649,682 yielded no disubstituted malonic derivative from di-*n*-butyl *cyclo*octylmalonate and methyl sulphate, the great majority of the original ester being recovered.

Diethyl cyclo*Oct-2-enylmalonate.*—(*a*) 3-Bromo*cyclo*octene (51 g.) was added during 20 min. to sodiomalonic ester (from 6·3 g. of sodium, 150 ml. of ethanol, and 28·6 g. of ethyl malonate). Titration of a 1-ml. sample 10 min. later showed that the reaction was 75% complete. The mixture was then heated on the steam-bath for 2 hr. Most of the ethanol was removed, the residue was treated with water and extracted with ether, and the extract was dried, and fractionated. The crude *ester* (36·3 g., 50%) on redistillation formed a colourless oil, b. p. 125—126°/1·5 mm., n_D^{22} 1·4691 (Found: C, 66·7; H, 8·8. $C_{15}H_{24}O_4$ requires C, 67·1; H, 9·0%).

(*b*) 1 : 2-Dibromo*cyclo*octane (176 g.) was added to sodiomalonic ester (from 30 g. of sodium, 400 ml. of ethanol, and 104 g. of ethyl malonate), and the whole stirred under reflux for 5 days. The ethanol was distilled off, the residue was diluted with water, and the product isolated in the usual manner. The yield of ester was 39%. A by-product (m. p. 76°) obtained in this reaction was ethanetetracarboxylic ester. Hydrolysis of either sample of *cyclo*oct-2-enylmalonic ester gave cyclo*oct-2-enylmalonic acid*, colourless needles (from water), m. p. 164—165° (decomp.) (Found: C, 62·3; H, 7·7%; equiv., 107. $C_{11}H_{16}O_4$ requires C, 62·3; H, 7·6%; equiv., 106).

Corresponding *cyclo*oct-1-enylmalonic esters could not be obtained from 1-bromo*cyclo*octene

and sodiomalonic esters by the methods used in the above preparations. From one of these experiments was isolated a small quantity of diethyl phloroglucinoldicarboxylate, m. p. 106—107° (Found: C, 53·2; H, 5·4; equiv., 273. Calc. for $C_{12}H_{14}O_7$: C, 53·3; H, 5·2%; equiv., 270), which is known to be formed from malonic ester and sodium ethoxide under certain conditions.

Barbituric Acid Derivatives.—The tabulated *compounds* (I) were prepared by standard methods.

					Found, %				Required, %			
No.	R′	R″	Y	M. p.	C	H	N	S	C	H	N	S
		R = *cyclo*octyl.										
1	H	H	O	254°	60·6	7·7	11·7	—	60·5	7·6	11·8	—
2	Me	H	O	262—263	62·2	8·0	10·9	—	61·9	8·0	11·1	—
3	Allyl	H	O	169—170	65·0	8·1	10·0	—	64·8	7·9	10·1	—
4	Me	Me	O	138	62·9	8·4	10·6	—	63·2	8·3	10·5	—
5	Me	H	S	166—167	57·9	7·1	10·5	12·0	58·2	7·5	10·5	11·9
		R = *cyclo*oct-2-enyl.										
6	H	H	O	225	60·9	6·9	11·8	—	61·0	6·8	11·9	—
7	H	H	S	246	57·6	6·4	—	—	57·1	6·4	—	—
8	Allyl	H	S	225—226	62·1	6·9	—	10·9	61·7	6·9	—	11·0

Compounds 3 and 8 were prepared from 1 and 7 respectively by shaking a solution of the barbituric acid in aqueous sodium hydroxide with allyl bromide for 48 hr. No. 2 could not be prepared from no. 1 under similar conditions with methyl iodide.

The sodio-derivatives were prepared by addition of the calculated amounts of alcoholic sodium hydroxide. Those of nos. 2, 6, and 8 were insoluble in ethanol and were isolated by filtration, whilst those of nos. 4, 5, and 7 were soluble and were isolated by evaporation *in vacuo*.

The authors thank Dr. S. A. Miller for his advice and the Directors of the British Oxygen Co. Ltd. for permission to publish this paper. They are indebted to Dr. G. F. Somers, The School of Pharmacy, London, W.C.1, for carrying out the tests for toxicity and narcotic action.

Research & Development Department,
The British Oxygen Company Ltd., London, S.W.19. [*Received, May 25th,* 1954.]

Sesquiterpenoids. Part IV. The Constitution of Carissone.*

By D. H. R. Barton and E. J. Tarlton.

[Reprint Order No. 5428.]

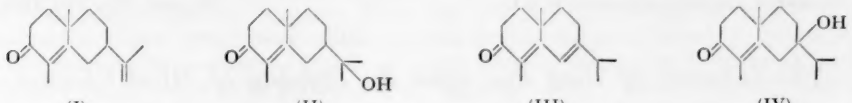
Dehydration of carissone under mild basic conditions, followed by conversion into the 2 : 4-dinitrophenylhydrazone in the usual way, gives β-cyperone 2 : 4-dinitrophenylhydrazone. Analogous dehydration of carissone 2 : 4-dinitrophenylhydrazone itself affords the α-cyperone derivative. On the basis of these observations the constitution (II) of carissone can be taken as established.

The isolation of an αβ-unsaturated ketone, carissone, $C_{15}H_{24}O_2$, from the roots of *Carissa lanceolata* (R. Brown) was reported recently by Mohr, Schindler, and Reichstein (*Helv. Chim. Acta*, 1954, **37**, 462). The infra-red spectrum of the compound revealed the presence of a hydroxyl group which, since it was stable to chromic acid, must be tertiary. The ultra-violet absorption spectrum ($\lambda_{max.}$ 250 mμ, ε 15,000) and the rotation ($[\alpha]_D$ +137° in $CHCl_3$) are reminiscent of those recorded (for summary see Simonsen and Barton, "The Terpenes," Vol. III, Cambridge Univ. Press, 1952) for α-cyperone (I) and it seemed to us that carissone might well be represented by the expression (II). Through the great kindness of Professor T. Reichstein, to whom we express our best thanks, in making available an adequate supply of carissone, it has been possible to adduce further evidence which has confirmed the correctness of our hypothesis.

Dehydration of carissone with phosphorus oxychloride in pyridine solution afforded an oil which, on conversion into the 2 : 4-dinitrophenylhydrazone in the usual way and

* Part III, *J.*, 1953, 3124.

careful chromatography of the product over alumina, gave the 2 : 4-dinitrophenylhydrazone of β-cyperone (III) (Bradfield, Gillam, Hegde, and Simonsen, *J.*, 1936, 667; Bradfield, Pritchard, and Simonsen, *J.*, 1937, 760; Adamson, McQuillin, Robinson, and Simonsen, *J.*, 1937, 1576; McQuillin, *J.*, 1951, 717) identical in all respects with a purified authentic specimen.* This identity establishes the carbon skeleton of carissone and the position of the unsaturated ketone grouping, and leaves undecided only the point of attachment of



(I) (II) (III) (IV)

the tertiary hydroxyl group. This tertiary hydroxyl group could be secured as in (IV) or, allowing for the ready acid-catalysed migration (Simonsen *et al.*, *locc. cit.*) of the ethylenic linkage in α-cyperone (I) to give β-cyperone (III), as in (II). The stability of carissone to aqueous-methanolic sodium hydroxide (Mohr, Schindler, and Reichstein, *loc. cit.*) contraindicates (IV). Furthermore, treatment of the 2 : 4-dinitrophenylhydrazone of α-cyperone (I) with acid of the concentration normally used in the preparation of 2 : 4-dinitrophenylhydrazones led to smooth conversion into the 2 : 4-dinitrophenylhydrazone of β-cyperone (III).

Decisive evidence in favour of structure (II) was obtained by transforming carissone into its 2 : 4-dinitrophenylhydrazone and dehydrating this with phosphorus oxychloride in pyridine solution (mild basic conditions). Careful chromatography of the product afforded α-cyperone 2 : 4-dinitrophenylhydrazone, identical in all respects with a purified authentic specimen.

Experimental

Ultra-violet absorption spectra were determined in $CHCl_3$ with the Unicam S.P. 500 Spectrophotometer. $[\alpha]_D$ are in $CHCl_3$.

α- and β-Cyperone 2 : 4-*Dinitrophenylhydrazones.*—Authentic α-cyperone 2 : 4-dinitrophenylhydrazone was carefully chromatographed over alumina, and the fractions of $\lambda_{max.}$ 395 mμ were combined. Recrystallised from chloroform–*iso*propyl ether, the pure material had m. p. 188—190°, $[\alpha]_D$ +414° (*c*, 0·0124), $\lambda_{max.}$ 395 mμ (ε 29,000). Authentic β-cyperone 2 : 4-dinitrophenylhydrazone, purified by chromatography and crystallisation from chloroform–ethanol, had m. p. 229—230°, $[\alpha]_D$ +831° (*c*, 0·0052), $\lambda_{max.}$ 415 mμ (ε 34,000).

Isomerisation of α- to β-Cyperone 2 : 4-*Dinitrophenylhydrazone.*—A solution of α-cyperone 2 : 4-dinitrophenylhydrazone (150 mg.) in ethanol (10 ml.). water (3 ml.), and concentrated sulphuric acid (3 ml.) was refluxed for 1 hr. Crystallisation of the product from chloroform–ethanol gave β-cyperone 2 : 4-dinitrophenylhydrazone (93 mg.), m. p. 230—232°, $[\alpha]_D$ +896° (*c*, 0·0053), $\lambda_{max.}$ 415 mμ (ε 34,000), undepressed in m. p. on admixture with the comparable material described above.

Dehydration of Carissone.—A solution of carissone (207 mg.) in anhydrous pyridine (5 ml.) and redistilled phosphorus oxychloride (1 ml.) was heated on the steam-bath for 1 hr. The oily product was treated with 2 : 4-dinitrophenylhydrazine (200 mg.) in ethanol (10 ml.), water (3 ml.), and concentrated sulphuric acid (2 ml.) under reflux. Chromatography of the product over alumina and elution with benzene gave dark red leaflets (120 mg.), m. p. 209—215°. Crystallisation from chloroform–ethanol afforded β-cyperone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 230—232°, $[\alpha]_D$ +882° (*c*, 0·0046), $\lambda_{max.}$ 415 mμ (ε 31,500).

Carissone 2 : 4-*Dinitrophenylhydrazone.*—Carissone (108 mg.) was converted into the 2 : 4-dinitrophenylhydrazone in the usual way. Chromatography over alumina and elution with ether–benzene (1 : 3), followed by crystallisation from chloroform–methanol, gave the pure 2 : 4-*dinitrophenylhydrazone* (125 mg.), m. p. 174—175°, $[\alpha]_D$ +538° (*c*, 0·0139), $\lambda_{max.}$ 392 mμ (ε 26,000) (Found : N, 13·3. $C_{21}H_{28}O_5N_4$ requires N, 13·45%).

Dehydration of Carissone 2 : 4-*Dinitrophenylhydrazone.*—A solution of this hydrazone (460 mg.) in anhydrous pyridine (5 ml.) and redistilled phosphorus oxychloride (1 ml.) was heated

* We express our best thanks to Professor Sir John Simonsen, F.R.S., and to Dr. L. N. Owen (Imperial College) for making available to us authentic specimens of α- and β-cyperone derivatives.

on the steam-bath for 1 hr. Chromatography of the product over alumina, elution with benzene–light petroleum (b. p. 40—60°) (1 : 3), and collection only of fractions with $\lambda_{max.}$ 395 mμ gave, after recrystallisation from chloroform–*iso*propyl ether, α-cyperone 2 : 4-dinitrophenylhydrazone (93 mg.), m. p. and mixed m. p. 188—190°, $[\alpha]_D$ +422° (*c*, 0·013), $\lambda_{max.}$ 395 mμ (ε 30,000).

This work was carried out whilst one of us (E. J. T.) was in receipt of a Beaverbrook Overseas Scholarship.

BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, May 31st*, 1954.]

The Influence of Ring Size upon the Stability of Metal Chelates.

By H. IRVING, R. J. P. WILLIAMS, D. J. FERRETT, and A. E. WILLIAMS.

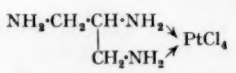
[Reprint Order No. 4385.]

Although the basic strength of the ligand is greater, the stability constants of the six-membered ring chelates of 1 : 3-diaminopropane with copper, nickel, and cadmium are lower than those of the corresponding five-membered ring chelate complexes of ethylene- or propylene-diamine. Similarly, β-alanine is found to form weaker metal complexes than α-alanine or glycine, despite its greater affinity for protons. The same behaviour characterises complexes of malonic and oxalic acid, and published data for a great variety of polydentate ligands support the generalisation that the stability of chelate complexes decreases with increasing ring size. Several factors which contribute to this behaviour are discussed.

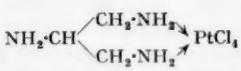
ALTHOUGH the relation between ring size and stability in *cyclo*paraffins and similar systems has provided one of the classical problems of organic chemistry, the superficially analogous problems presented by chelate-ring formation among inorganic co-ordination compounds have excited little interest. Relatively few attempts have been made to correlate their stability with ring size, with the nature of the metal involved and the orbitals available, or with the electronegativities of the co-ordinating atoms and the basic strength and molecular geometry of the ligand molecules.

Evidence that stability diminished with ring size has been based upon the facts that Bailar and Work (*J. Amer. Chem. Soc.*, 1946, **68**, 233) experienced more difficulty in making cobaltic tris-complexes with 1 : 3-diaminopropane ("dmp"; $NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$) or *neo*pentanediamine ($NH_2{\cdot}CH_2{\cdot}CMe_2{\cdot}CH_2{\cdot}NH_2$) than with ethylenediamine ("en"; $NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$), that Pfeiffer and Haiman (*Ber.*, 1903, **36**, 1064) experienced similar difficulties with copper, and that Drew and Tress (*J.*, 1933, 1335) found platinum would co-ordinate with ethylenediamine and "less readily" with 1 : 3-diaminopropane, while higher diamines formed only amorphous, ill-defined products. The value of such evidence, however, is vitiated because there is an obvious confusion here between the "ease of formation" of a ring-system and its stability when once obtained.

More satisfactory evidence is provided by Mann's demonstration (*J.*, 1926, 2681) that the complex formed by platinic chloride and 1 : 2 : 3-triaminopropane could be resolved; this proved that a five-membered ring was present in (I) and, by implication, that this must be more stable than the alternative structure (II) which could have contained a six-membered ring.



(I)



(II)

The fundamental difference between chelate ring complexes in organic chemistry and, *e.g.*, polymethylene rings is that the reactions leading to ring formation are reversible in the former cases. Thus it becomes possible in principle to determine the equilibrium constant and free-energy change of the inorganic chelating reaction from measurements of the concentrations of metal, ligand, and chelated complex in equilibrium. Proceeding on these lines we have measured the stability constants of several inorganic complexes containing

five- and six-membered rings. Supplemented by data in the literature, the results confirm the hypothesis that increase in chelate ring size is accompanied by a decrease in stability.

From measurements at a series of temperatures it is possible to analyse the free-energy change of a chelation reaction into its component entropy and heat terms. The latter may also, with advantage, be determined by direct calorimetry. In a further paper (Irving and Dickens, in preparation) such thermodynamic data for many of the complexes referred to in this paper will be presented and discussed.

Chelate Rings formed by Aliphatic Diamines.—By the Calvin–Bjerrum technique as previously described (Irving and Griffiths, *J.*, 1954, 213; Irving and Rossotti, *J.*, 1954, 2904) the acid dissociation constants of 1 : 3-diaminopropane were found to be given by $pK_{BH^+} = 10{\cdot}72$ and $pK_{BH_2^{++}} = 8{\cdot}98$ in 0·1N-potassium chloride at 25°. Compared with that of ethylenediamine (Table 1) the increased chain length has caused a significant increase in basic strength while, as expected from statistical and other considerations, the difference between pK_{BH^+} and $pK_{BH_2^{++}}$ is considerably reduced (cf. Schwarzenbach, Maissen, and Ackermann, *Helv. Chim. Acta*, 1952, **35**, 2333). With hexamethylenediamine the difference between the two thermodynamic constants at 25° is only 1·1 logarithmic units (Everett and Pinsent, *Proc. Roy. Soc.*, 1952, *A*, **215**, 417).

TABLE 1.

	Ethylene-diamine	Propylene-diamine	1 : 3-Di-amino-propane
Proton complexes			
pK_{BH^+}	10·17[a]	9·83[b]	10·72[c,d]
$pK_{BH_2^{++}}$	7·44	7·07	8·98
ΔpK	2·73	2·76	1·74
Cadmium complexes			
$\log \beta_2$	10·22[a]	9·97[b]	7·42[b]
$\log \beta_3$	12·29	12·12	8·03
$\frac{1}{2} \log \beta_2/pK_{BH^+}$	0·50	0·50	0·35
Copper complexes			
$\log K_1$	10·73[a]	10·58[b]	9·77[c]
$\log K_2$	9·30	9·08	7·17
$\log \beta_2$	20·03[a]	19·66[a]	16·94[c,f]
$\log K_1/K_2$	1·43	1·50	2·60
$\frac{1}{2} \log \beta_2/pK_{BH^+}$	0·98	1·0	0·79
Nickel complexes			
$\log K_1$	7·66[g]	7·41[b]	6·38[i]
$\log K_1/pK_{BH^+}$	0·76	0·76	0·6

[a] Bjerrum and Nielsen, *Acta Chim. Scand.*, 1948, **2**, 297; glass-electrode measurements in N-potassium nitrate. [b] Carlson, McReynolds, and Verhoek, *J. Amer. Chem. Soc.*, 1945, **67**, 1334; glass-electrode measurements at 30° in 0·5M-neutral salt background. [c] Present authors; glass electrode at 25° in 0·1M-potassium chloride. [d] Schwarzenbach, Maissen, and Ackermann (*loc. cit.*) report 10·64, 8·88, and 1·76 for 0·1N-sodium nitrate at 20°. [e] Laitinen, Onstott, and Bailar, *J. Amer. Chem. Soc.*, 1949, **71**, 1550, obtained the values $\log \beta_2 = 19{\cdot}72$ for ethylenediamine and 20·17 for propylenediamine by polarography in 0·1N-potassium nitrate at 25°. [f] Polarographic value (ref. *h*) = 16·67. [g] Bjerrum and Andersen, *Kgl. Danske Videnskab.*, 1945, **22**, 1773; glass-electrode measurements in N-potassium nitrate at 25°. [h] Present authors; polarography at 25° in 0·1M-potassium chloride. [i] Bjerrum, personal communication.

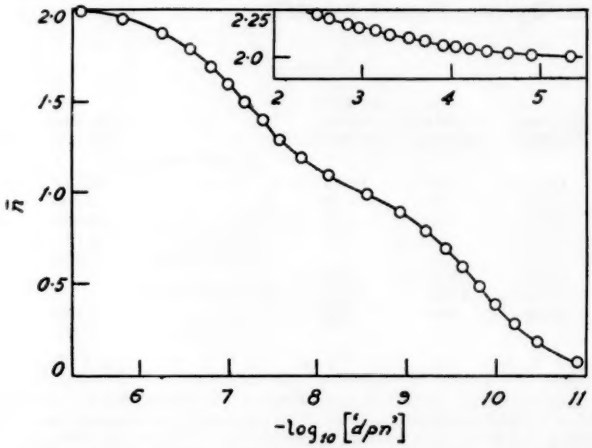
For the complex species ML_n the stability constant is defined by $K_n = [ML_n]/[ML_{n-1}][L]$, and $\beta_n = K_1K_2 \ldots K_n$.

Difficulty was at first encountered in measuring the stability constants of the copper complexes of 1 : 3-diaminopropane owing to the separation of basic material during the titration. This was overcome by considerably reducing the concentration of metal used. For the same reason barium chloride was used in place of magnesium chloride when measuring the dissociation of the ligand itself. For free ligand exponents less than 4·5 (Fig. 1, inset) the degree of formation rose slightly above two. This might suggest the co-ordination of a third nolecule of diamine, possibly through one nitrogen atom only, as Bjerrum and Nielsen (*loc. cit.*) have postulated in the case of ethylenediamine and copper. This possibility was not supported by spectrophotometric measurements, for no difference could be detected between the spectra in the visible region of solutions containing copper and diamine in the ratios 1 : 4 and 1 : 12. The discrepancy may arise from the effect of high diamine concentrations on the liquid–liquid junction potentials which are assumed to be constant throughout the titration. Independent determination of the stability of the copper–1 : 3-diaminopropane complex by a polarographic method gave the value $\log \beta_2 = 16{\cdot}67$ in 0·1M-potassium nitrate at 25°, confirming the potentiometric measurements. The values

log $\beta_2 = 7{\cdot}42$ and log $\beta_3 = 8{\cdot}03$ obtained by this technique for cadmium and 1 : 3-diaminopropane are decidedly lower (Table 1) than the values for ethylenediamine.

It has been shown (Irving and Griffiths, *loc. cit.*) that methyl substitution at one or both of the nitrogen atoms of ethylenediamine increases the basic strength but, through the operation of steric factors, decreases the stability of the metal complexes. Table 1 shows that methyl substitution in the aliphatic chain has remarkably little effect on the dissociation constants of either proton or metal complexes of ethylenediamine (for further data, see Carlson, McReynolds, and Verhoek, *loc. cit.*). Increased chain length, by increasing ring size, brings about a notable decrease in stability notwithstanding the increased basicity of the ligand, *i.e.*, its affinity for protons. This is depicted quantitatively by the fall in the quotient $\frac{1}{2}\log \beta_2/pK_{BH^+}$. The steric hindrance to the co-ordination of a second molecule of diamine is measured by the value of log K_1/K_2 which increases on passing from "en" and "pn" to "dmp." With cadmium the effect of exchanging "dmp" for "en" can be seen in the ratio log β_3/β_2.

FIG. 1. *The formation curve for copper and* 1 : 3-*diaminopropane at* 25°



With water as solvent it does not appear to be possible to measure the stability constants of chelates of 1 : 3-diaminopropane with bivalent ions of complexing power appreciably lower than that of copper, nickel, or cadmium; with diamines capable of forming seven- or higher-membered rings, measurements are impossible even with copper. This can be explained as follows. As the separation between the terminal groups of a diamine is increased the tendency to chelate with metals decreases, but the tendency to bind protons increases. For any arbitrary values of C_M and C_L, the total concentrations of metal and ligand in the system, the first effect of increasing chain length will be to reduce the degree of formation, $\bar{n}$, of the system, since individual values of the stability constants K_n are decreased (Irving and Williams, *Analyst*, 1952, **77**, 257). This will cause an increase in the concentration [M] of uncomplexed cations, while the pH will rise owing to the increased interaction of ligand (no longer complexed to metal) with protons derived from the solvent. The effects are co-operative in favouring the formation of metal hydroxides or basic complexes. Furthermore, with increasing chain lengths the ends of a bidentate ligand, Z, can function increasingly as monodentate ligands. This favours the formation of bimetallic complexes, *e.g.*, M·Z·M, or binuclear complexes, *e.g.*, M$\begin{smallmatrix}\swarrow Z \searrow \\ \nwarrow Z \nearrow\end{smallmatrix}$M, and greatly increases the difficulty of interpreting the experimental data (cf. Schwarzenbach, Maissen, and Ackermann, *loc. cit.*; Schwarzenbach, Ackermann, Maissen, and Anderegg, *Helv. Chim. Acta*, 1952, **35**, 2337).

When an aliphatic diamine is incorporated into a polydentate ligand the over-all stability may be increased sufficiently to permit the stability of five-, six-, and even seven-membered rings to be compared even when using ions of lower co-ordinating tendencies than those of the transition metals.

Table 2 shows that the homologues of ethylenediaminetetra-acetic acid, ($n = 1$) are almost identical in basic strength. However "Enta" (Fig. 2; $n = 1$, $m = 1$) derived from ethylenediamine gives five five-membered rings on chelation and forms complexes with magnesium, calcium, strontium, and barium which are more stable by some 4—5 kcal. than those formed by the homologue (Fig. 2; $n = 2$, $m = 1$) derived from 1 : 3-diaminopropane which forms one six- and four five-membered rings. In the exceptionally strong calcium complexes the further decrease in stability as seven- and eight-membered rings replace the five-membered chelate formed by "Enta" is convincingly shown. The diamine rings under discussion will certainly be strainless, and while this might also be

FIG. 2.

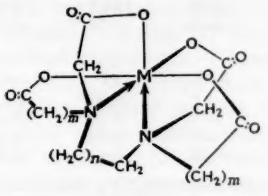
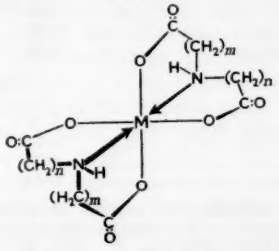


FIG. 3.



expected when the relevant nitrogen atoms are attached to a *cyclo*hexane ring as in the second group of compounds in Table 2, yet other stereochemical factors combine to produce a marked fall in stability when the five-membered ring formed by 1 : 2-diamino*cyclo*hexane-tetra-acetic acid with calcium and magnesium is replaced by the six- and seven-membered rings formed by its 1 : 3- and 1 : 4-isomers.

TABLE 2.

$A_2N{\cdot}[CH_2]_n{\cdot}CH_2{\cdot}NA_2$ [a] ($A = CH_2{\cdot}CO_2H$)	pK_1	pK_2	pK_3	pK_4	log K in 0·1N-KCl at 20° for Mg	Ca	Sr	Ba
$n = 1$	2·0	2·67	6·16	10·26	8·69	10·59	8·63	7·76
$n = 2$	2·0	2·67	7·91	10·27	6·02	7·12	5·18	4·24
$n = 3$	1·9	2·66	9·07	10·45	—	5·05	—	—
$n = 4$	2·2	2·79	9·50	10·58	—	4·60	—	—
1 : 2-$C_6H_{10}(NA_2)_2$ [b, c] ...	2·4	3·5	6·1	11·7	10·3	12·50	—	8·0 [d]
1 : 3- ,, ...	1·8	2·6	8·6	10·9	4·64	4·77	—	—
1 : 4- ,, ...	2·1	2·5	9·0	10·9	4·30	4·19	—	—

[a] Schwarzenbach and Ackermann, *Helv. Chim. Acta*, 1947, **30**, 1798; 1948, **31**, 1029. [b] C_6H_{10} = *cyclo*Hexylene residue. [c] *Idem, ibid.*, 1949, **32**, 1682. [d] Unpublished work by Schwarzenbach and Anderegg, quoted by Schwarzenbach (*loc. cit.*).

Chelate Rings formed by Amino-acids.—The most direct comparisons can be made between the five-membered chelates formed by glycine ("gl"; $NH_2{\cdot}CH_2{\cdot}CO_2H$) or α-alanine ("α-al"; $NH_2{\cdot}CHMe{\cdot}CO_2H$) and the six-membered chelates of β-alanine ("β-al"; $NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$). Although β-alanine proves to be a stronger base than glycine (Table 3), titrations with the glass electrode and polarographic measurements establish that its copper, nickel, zinc, and cobalt complexes are appreciably weaker. This is best shown by the falling values of the quotient $\frac{1}{2}\log\beta_2/pK_{ZH^{\pm}}$ (Table 3).

As with the diamines (see above) confirmatory evidence of the decrease of stability with increasing ring size is provided by complexes of polydentate amino-acids. Table 4 shows the fall in stability when the tridentate α-alaninediacetic acid ($NA_2{\cdot}CHMe{\cdot}CO_2H$; "Cim-α"), which forms three five-membered rings with an alkaline-earth metal, is replaced by β-alaninediacetic acid ($NA_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$; "Cim-β") which forms two five-membered and

one six-membered ring. The same phenomenon is shown by the phosphonic acids " Pim-α " and " Pim-β." In these instances the respective pairs of chelating partners are of much the same basicity, so the observed decrease in stability must be due predominantly to ring enlargement. Unambiguous proof follows from the data of Table 4 for the set of related compounds iminodiacetic acid (" Imda "), iminoaceticpropionic acid (" Impa ") and iminodipropionic acid (" Imdp "), for although the basicities increase regularly in this order the

TABLE 3.

	Glycine (" gl ")	α-Alanine (" α-al ")	β-Alanine (" β-al ")
$pK_{ZH_2^+}$	2·24 [a]	2·34 [b]	3·52 [a]
$pK_{ZH^\pm}$	9·85	9·87	10·26

	Nickel complexes			Copper complexes		
	gl	α-al	β-al	gl	α-al	β-al
$\log K_1$	5·73 [a]	5·96 [d]	4·63 [a]	8·12 [a]	8·18 [b]	7·13 [a]
$\log K_2$	4·76	4·70	3·40	6·91	6·65	5·47
$\log K_1/K_2$	0·97	1·26	1·23	1·21	1·53	1·66
$\log \beta_2$	10·49	10·66	8·03	15·03	14·83	12·60
$\frac{1}{2} \log \beta_2/pK_{ZH^\pm}$	0·53	0·54	0·39	0·76	0·75	0·61

	Zinc complexes			Cobalt complexes		
	gl	α-al	β-al	gl	α-al	β-al
$\log K_1$	5·16 [a]	5·16 [b]	~4 [a]	4·95 [b]	4·83	—
$\log K_2$	4·34	4·34	—	3·99	3·95	—
$\log \beta_2$	9·50	9·50	—	8·94	8·78	~7
$\frac{1}{2} \log \beta_2/pK_{ZH^\pm}$	0·48	0·48	<0·34	0·46	0·45	<0·33

[a] A. E. Williams (this paper); glass-electrode measurements at 20°; additional measurements are quoted in ref. *b*. [b] Mellor and Maley, *Austral. J. Sci. Res.*, 1948, **2**, 579; potentiometric titrations at 25°. [c] Albert, *Biochem. J.*, 1950, **47**, 531; potentiometric titrations at 20°. [d] Monk, *Trans. Faraday Soc.*, 1951, **47**, 285, 297; values for 25°. [e] Ferrett (this paper) obtained $\log \beta_2 = 12{\cdot}65$ by polarography at 25° in 0·1M-potassium nitrate; Albert (ref. *c*) reports $\log \beta_2 = 12{\cdot}90$, which is reduced to 12·8 if the value $pK_{ZH^\pm} = 10{\cdot}3$ is employed.

TABLE 4. *Stability constants of complexes formed by polydentate amino-acids.*

(*a*) Proton complexes

Formula	Trivial name	pK_1	pK_2	pK_3	pK_4	Ref.
NA_3 *	Cim-α	1·89	2·49	9·73	—	*a*
NA_2B †	Cim-β	2·06	3·69	9·66	—	*a*
$NA_2{\cdot}CH_2{\cdot}PO(OH)_2$	Pim-α	2·0	2·25	5·57	10·76	*a*
$NA_2{\cdot}CH_2{\cdot}CH_2{\cdot}PO(OH)_2$	Pim-β	1·95	2·45	6·54	10·46	*a*
NHA_2	Imda	2·54	9·12	—	—	*b*
NHAB	Impa	3·61	9·46	—	—	*c*
NHB_2	Imdp	4·11	9·61	—	—	*b*
$NH_2{\cdot}CHA{\cdot}CO_2H$	Aspa	3·68	9·46	—	—	*c*
$NA_2{\cdot}CH_2{\cdot}CH_2{\cdot}NA_2$	Enta	2·0	2·67	6·16	10·26	*e*
$NAB{\cdot}CH_2{\cdot}CH_2{\cdot}NAB$	Endap	3·0	3·79	5·98	9·83	*d*

(*b*) Metal complexes

Ligand		Mg	Ca	Sr	Ba	Fe	Co	Ni	Cu	Zn	Cd	Pb	Ref.
Cim-α	$\log K_1$	5·41	6·41	4·94	4·82	—	—	—	—	10·49	—	—	*a*
Cim-β	$\log K_1$	5·28	5·04	3·87	3·40	—	—	—	—	10·07	—	—	*a*
Pim-α	$\log K_1$	6·28	7·18	5·59	5·35	—	—	—	—	—	—	—	*a*
Pim-β	$\log K_1$	6·33	5·44	4·10	3·64	—	—	—	—	11·24	—	—	*a*
Imda	$\log K_1$	3·66	3·41	—	1·67	5·8 [f]	6·98	8·25	10·55	7·02 [f]	5·33	—	*b*
	$\log K_2$	—	—	—	—	4·3	5·34	6·35	5·65	5·14	4·18	—	*b*
Impa	$\log K_1$	—	—	—	—	—	6·15	7·34	10·48	6·21	4·53	—	*c*
	$\log K_2$	—	—	—	—	—	4·20	5·23	4·45	4·31	3·16	—	*c*
Imdp	$\log K_1$	—	—	—	—	—	4·94	6·16	9·44	4·95	3·55	—	*b*
	$\log K_2$	—	—	—	—	—	3·25	3·77	3·68	precipitation when $n > 0{\cdot}5$			
Aspa	$\log K_1$	—	—	—	—	—	5·87	7·10	8·54	5·81	4·37	—	*c*
	$\log K_2$	—	—	—	—	—	4·28	5·27	6·78	4·31	3·11	—	*c*
Enta	$\log K_1$	8·7	10·6	8·6	7·8	14·3 [g]	16·1	18·4	18·3	16·1	16·4	18·2	*e*
Endap	$\log K_1$	6·9	—	—	—	—	14·9	15·5	16·3	14·5	11·8	13·2	*d*

* A = $CH_2{\cdot}CO_2H$. † B = $CH_2{\cdot}CH_2{\cdot}CO_2H$.

[a] Schwarzenbach and Ruckstuhl, *Helv. Chim. Acta*, 1949, **32**, 1175. [b] Chabareck and Martell, *J. Amer. Chem. Soc.*, 1952, **74**, 5052. [c] *Idem, ibid.*, p. 6021. [d] *Idem, ibid.*, p. 6228. [e] Schwarzenbach and Freitag, *Helv. Chim. Acta*, 1951, **34**, 1503. [f] Schwarzenbach and Ruckstuhl, *ibid.*, 1952, **35**, 2346. [g] Schwarzenbach and Heller, *ibid.*, 1951, **34**, 576.

stabilities of the metal complexes decrease as the two five-membered rings found in complexes of Imda (Fig. 3; $n = m = 1$) are replaced successively by one five- and one six-membered ring in Impa (Fig. 3; $n = 1$, $m = 2$) and two six-membered rings in complexes formed by Imdp (Fig. 3, $n = m = 2$). The effect is clear cut with complexes of cobalt, nickel, zinc, and cadmium, and for the attachment of both the first and the second molecule of these bidentate ligands.

Values of log K_1 in the case of copper again demonstrate the fall in stability as first one and then the second five-membered is replaced by a six-membered ring. The anomalous low values of log K_2 arise from copper's lower maximum co-ordination number of four, in consequence of which only four chelate groups are present in the 1 : 2-complex in contrast to the six chelate rings formed by the neighbouring metals (Fig. 3). The abnormally small decrease in log K_2 in passing from Imda (16·20) to Impa (15·38) is similarly explained; for while the 1 : 1 complex of Impa possesses both a five- and a six-membered ring, since only two chelate rings are tolerated by copper, the formation of the 1 : 2 complex will probably involve two 5-rings formed from the α-amino-acid moiety of each ligand, the residual $-CH_2{\cdot}CH_2{\cdot}CO_2-$ being directed away form the central ion. On the assumption that $Cu(Imdp)_2$ is normally constructed from two six-membered rings, the effect of ring enlargement is clear. Comparisons of Aspa and Impa, both of which can form one five- and one six-membered ring, have been made by Chabarek and Martell (*loc. cit.*).

Data for the hexadentate ligands ethylenediaminetetra-acetic acid (Enta; Fig. 2; $n = 1$, $m = 1$) and ethylenediaminediaceticdipropionic acid (Endap; Fig. 2; $n = 1$, $m = 2$) illustrate again the fall in stability on ring enlargement in the complexes with magnesium, cobalt, zinc, copper, cadmium, and lead (Table 4). For all these polydentate ligands the stability order Fe < Co < Ni < Cu > Zn is strictly obeyed for values of log K_1, thus supplementing the results previously discussed by Irving and Williams (*J.*, 1953, 3192). Minor regularities in the case of copper (especially for log K_2) result from its lower co-ordination number and from changes in the type of rings formed when a second molecule of ligand becomes attached (Irving and Williams, *loc. cit.*; Chabarek and Martell, *loc. cit.*). Albert's results for polyaminocarboxylic acids (*Biochem. J.*, 1952, **50**, 690) afford further examples of decrease of stability accompanying ring enlargement, although the interpretation of the pH titrations is complicated by the many alternative possible modes of chelation whose relative probabilities will depend in a complicated way upon the pH of the solution, the dissociation constants of the ligands, the relative amounts of metal and ligand as well as their absolute concentrations, and the permitted or favoured stereochemistry (cf. Williams, *Nature*, 1953, **171**, 304).

Chelate Rings formed by Carboxylic Acids.—Attention has often been drawn to the general decrease in stability of complexes of certain metals when malonic acid replaces oxalic acid as the bidentate partner (cf. James and Peacock, *J.*, 1951, 2233; Schwarzenbach, *loc. cit.*; Irving, "Discussion on Co-ordination Chemistry," I.C.I. Report BRL/146, September 1950; Williams, *J.*, 1952, 3770). Table 5 summarises the available data for dicarboxylic acids and shows that the stability decrease persists for the 5-, 6-, and 7-membered rings formed by oxalate, malonate, and succinate ions with a wide variety of bivalent cations. That tervalent ions behave similarly is shown by the data for La^{3+} in Table 5, and by the values $[Mn(C_2O_4)_3^{3-}]/[Mn(C_2O_4)_2(H_2O)_2^{-}][C_2O_4^{2-}] = 260$, and $[Mn(C_3H_2O_4)_3^{3-}]/[Mn(C_3H_2O_4)_2(H_2O)_2^{-}][C_3H_4O_2^{2-}] = 18$ obtained spectrophotometrically at 0° for the oxalato- and malonato-complexes of Mn^{3+} by Cartledge and Ericks (*J. Amer. Chem. Soc.*, 1936, **58**, 2065) and Cartledge and Nichols (*ibid.*, 1940, **62**, 3057).

With further increase in chain length there appears some indication that the stability of metal complexes derived from carboxylic acids, $HO_2C{\cdot}[CH_2]_n{\cdot}CO_2H$, passes through a minimum when $n = 4$. Whether this effect is real or not cannot readily be established, for the values given in the last three rows of Table 5 are obtained as the differences between averaged stability constants, themselves obtained by a variety of methods and recalculated to a common basis (25° and $\mu = 0$) from the often widely different conditions prevailing in the original measurements. Although polydentate carboxylic acids of the type $HO_2C{\cdot}CH[(CH_2)_n{\cdot}CO_2H]_2$ have not been studied systematically, Schubert and Lindenbaum (*J. Amer. Chem. Soc.*, 1952, **74**, 3529) report for tricarballylic acid ($n = 1$) and carboxy-

pimelic acid ($n = 2$) the values log K_1 (calcium) = 1·82 and 1·59 and for log K_1 (strontium) = 1·68 and 1·54, confirming the lower stability associated with the larger ring.

TABLE 5. *Stability constants of metal–dicarboxylate ion complexes.*

Ligand	pK_1	pK_2	Mg	Ca	Sr	Ba
Acetate	4·75	—	1·05	1·0	0·97	0·93
Oxalate	1·23	4·19	3·43, 3·25 [a]	3·00	2·54	2·33
Malonate	2·85	5·66	2·85, 2·60 [a]	2·50, 2·16 [a]		1·71, 1·93,[a] 2·13 [c]
Succinate	4·20	5·60	1·90,[a] 2·40 [f]	1·90 [a]	—	2·08,[c] 1·73,[a] 1·96 [f]
Glutarate	4·34	5·42	1·78 [a]	1·76 [a]	—	2·04 [c]
Adipate	4·43	5·42	—	2·19 [f]	—	1·92,[c] 1·85 [f]
Ligands exchanged						
Oxalate/malonate	—	—	0·6	0·7	—	0·4
Malonate/succinate	—	—	0·8	0·2	—	0·0
Succinate/glutarate	—	—	0·1	0·4	—	−0·1
Glutarate/adipate	—	—	—	−0·4	—	0·2

Ligand	Mn	Co	Ni	Cu	Zn	Cd	La^{3+}	$Co(NH_3)_6^{3+}$
Acetate	—	—	0·67 [b]	1·66 [i]	1·57	—	—	—
Oxalate	3·89	4·70	5·30	6·12 [b]	4·89	3·89	—	3·40 [e]
					5·00	4·00 [e]		
Malonate	3·29	3·72	4·01	5·80 [e]	3·68	3·25	4·89 [e]	3·54 [e]
				5·73 [d]	3·75 [g]			
Succinate	—	—	—	3·33 [e]	2·48 [a]	—	3·96 [e]	2·94 [e]
Glutarate	—	—	—	3·16 [e]	2·30 [a]	—	3·82 [e]	3·17 [e]
Adipate	—	—	—	3·38 [e]	—	—	4·10 [e]	3·35 [e]
Ligands exchanged								
Oxalate/malonate	0·6	1·0	1·3	0·4	1·2	0·7	—	−0·1
Malonate/succinate	—	—	—	2·4	1·2	—	0·9	0·6
Succinate/glutarate	—	—	—	0·2	0·2	—	0·1	−0·2
Glutarate/adipate	—	—	—	−0·2	—	—	−0·3	−0·2

Thermodynamic acid dissociation constants from Jeffery and Vogel (*J.*, 1935, 21) and Speakman (*J.*, 1940, 855).

[a] Cannan and Kibrick, *J. Amer. Chem. Soc.*, 1938, **60**, 2314. [b] Ives, *J.*, 1933, 1360. [c] Peacock and James, *J.*, 1951, 2233. [d] Ives and Riley, *J.*, 1931, 1998. [e] Vosburgh and Beb, *J. Amer. Chem. Soc.*, 1940, **62**, 1028. [f] Topp and Davies, *J.*, 1940, 87. [g] James, *J.*, 1951, 153. [h] *Idem, Acta Chem. Scand.*, 1952, **6**, 1200. [i] Fronaeus, *ibid.*, 1951, **5**, 859.

Unless stated to the contrary the metal stability constants are those quoted by Denny and Monk from many sources (*Trans. Faraday Soc.*, 1951, **47**, 992, and refs. therein). Data from refs. *a*, *d*, and *f* have been corrected to $\mu = 0$ by Peacock and James (ref. *c*).

Discussion.—From the foregoing it may be concluded that the decrease in stability in replacing five- by six-membered rings of the same type is a general phenomenon shown by all metals and all polydentate ligands; further ring enlargement leads to still greater reduction in stability. Complexes of silver with aliphatic diamines, $NH_2{\cdot}[CH_2]_n{\cdot}NH_2$ form a noteworthy exception to this generalisation as may be seen from the following values valid for 20° and $\mu = 0{\cdot}1$ (Schwarzenbach, *Helv. Chim. Acta*, 1953, **36**, 23):

n	2	3	4	5
log K_1	4·7 ± 0·1	5·5 ± 0·07	5·90 ± 0·1	5·95 ± 0·1

The anomaly is readily explicable, for, since silver tends to form linear complexes, *e.g.*, $NH_3 \rightarrow Ag^+ \leftarrow NH_3$ and NC–Ag^-–CN, considerable strain will accompany the attempt to bridge the coaxial co-ordination positions with ethylenediamine. This strain will be reduced as n increases, but the consequent gain in stability will be offset to an increasing extent by the opposing effect of ring-enlargement already noted.

The "chelate effect," *i.e.*, the gain in stability when n molecules of a monodentate ligand are replaced by a single molecule of an n-dentate ligand, has been interpreted by Schwarzenbach (*ibid.*, 1952, **35**, 2344) as essentially an entropy effect. His semi-quantitative treatment, based on the volume, J, swept out by a ligand (*e.g.*, a diamine) co-ordinated to a metal only by one end, correctly predicts the observed decrease in stability with ring enlargement—but it underestimates its magnitude. Thus for the change from ethylenediamine to 1 : 3-diaminopropane the calculated increase in J (*loc. cit.*, p. 2354) is from 200 to 460 Å^3, corresponding to a decrease in stability of about 0·4 logarithmic unit. This is

considerably less than the observed values of 1·0 for copper and 1·3 for nickel (Table 1), and very much less than the values 2·7 for magnesium, 3·5 for calcium, 3·4 for strontium, and 3·5 for barium observed when the chelating diamine forms part of a more complex structure (Table 2). The predicted change in chelation energy on passing from a six- to a seven-membered ring is about 0·3 logarithmic unit, but the values found experimentally are again larger.

Actual values for the chelate effect cannot be calculated for amino-acids for lack of suitable reference data for monodentate ligands. However, on replacement of β-alanine by α-alanine the gain in chelation energy in logarithmic units per molecule chelated is 0·9 in the case of cobalt, 1·3 with nickel, 1·4 for copper, and 1·0 for zinc (Table 3). On Schwarzenbach's theory the magnitude of this effect could scarcely exceed 0·5 unit. Values for log β_2 corresponding to the attachment of two acetate ions would be needed to calculate the chelate effect for metal–dicarboxylate ion complexes, but hitherto data have been lacking. However, by using the value log $\beta_2 = 2{\cdot}65$ for the cupric–diacetate complex (Fronaeus, *Acta, Scand. Chem.*, 1951, **5**, 859), the magnitude of the chelate effect is given by Chel = log K_1 (oxalate) − log β_2 (acetate) = 3·47. Similarly, using the value log $\beta_2 = 1{\cdot}26$ for the nickel–diacetate ion complex we obtain Chel = 4·0. For both metals the effect is large and quite outside the range predictable by Schwarzenbach's theory.

Implicit in Schwarzenbach's theory is the simplifying assumption that there is no substantial heat change when two molecules of a monodentate ligand are replaced by a ring-system terminating in groups of the same type. Explicitly for such reactions as

$$M^{n+}, \text{aq.} + 2NH_3 \longrightarrow M(NH_3)_2^{n+}, \text{aq.} + 2H_2O \quad . \quad . \quad . \quad (1)$$

$$M^{n+}, \text{aq.} + \text{en} \longrightarrow M\,\text{en}^{n+}, \text{aq.} + 2H_2O \quad . \quad . \quad . \quad . \quad (2)$$

leading to the ligand exchange equation

$$M(NH_3)_2^{n+}, \text{aq.} + \text{en} \longrightarrow M\,\text{en}^{n+}, \text{aq.} + 2NH_3 \quad . \quad . \quad . \quad . \quad (3)$$

it is necessary to postulate that $\Delta H_1 \cong \Delta H_2$, so that $\Delta H_3 \cong 0$ or at least $\Delta H_3 \ll T\Delta S_3$, so that the value of the chelate effect (Chel = log K_3 = log K_2/K_1) is effectively determined by entropy considerations. From such an assumption there inevitably follows the conclusion that the magnitude of the chelate effect, and the magnitude of the stability decreases consequent upon ring enlargement, should be independent of the metal atoms involved—"Der Chelateffekt ist in der Tat unabhängig, oder weitgehend unabhängig von der Haftfestigkeit der einzelnen Ligandgruppe."

Experimental data do not support this generalisation. Among the more stable chelates of the transition metals the magnitude of the chelate effect can often be closely related to their individual stabilities. Thus for Co^{++}, Ni^{++}, and Cu^{++} we find linear relations

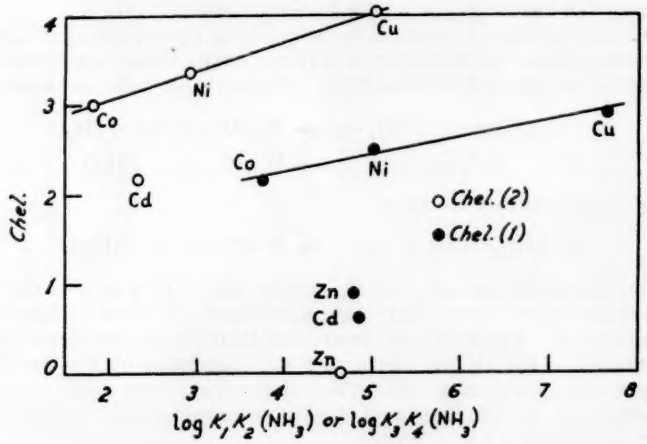
$$\text{Chel (1)} = \log K_1(\text{en})/K_1K_2(NH_3) = 0{\cdot}20 \log K_1K_2(NH_3) + 1{\cdot}40$$
$$\text{Chel (2)} = \log K\,(\text{en})/K_3K_4(NH_3) = 0{\cdot}32 \log K_3K_4(NH_3) + 2{\cdot}43$$

For these three metals Chel (1) is materially less than Chel (2). For cobalt and nickel we have Chel (3) = log $K_3(\text{en})/K_5K_6(NH_3) = 3{\cdot}54$ and 3·50, respectively, which represent still further increases of stability. While it is striking that the changes in the magnitude of the chelate effect increase for cobalt, nickel, and copper in the order in which these elements appear in the Irving–Williams series (*J.*, 1953, 3192), values of Chel (1) and Chel (2) for metals outside this series show no such linear relation to the stability of the reference ammonia complexes (Fig. 4). On the other hand, values of log K_1(α-alanine)/K_1(β-alanine) follow the Irving–Williams order (p. 3499). Such variations can scarcely be coincidental, and the fact that they are not predictable, even qualitatively, by Schwarzenbach's theory suggests that the latter is oversimplified. In a further paper (Irving and Dickens, in preparation) thermochemical measurements will be presented which will prove that in many cases where transition metals form complexes with formally uncharged diamines, the heat of reaction (i) differs from the heat change when two molecules of ammonia are co-ordinated, (ii) depends on the chain length of the ligand, (iii) varies with the nature of

the metal atom, and (iv) may contribute as substantially to the free-energy change as do various entropy terms.

In complexes involving neutral ligands there is no change during reaction in the formal charge on the ionised species. But in complexes formed by amino-acids or dicarboxylate ions, large entropy changes of some 25—100 cal./degree will be superimposed upon those due to other factors because the ordered arrangement of solvent around the ions is reduced on production of an uncharged (or lower charged) chelate complex. Thus for magnesium malonate $\Delta H_{298} = +3{\cdot}1$ kcal., while $T\Delta S = +7{\cdot}0$ kcal. (Evans and Monk, *Trans. Faraday Soc.*, 1952, **48**, 934), and for zinc malonate $\Delta H_{298} = +3{\cdot}06$ kcal. and $T\Delta S = +8{\cdot}17$ kcal. (James, *J.*, 1951, 153). Here the entropy increase is sufficient to overcome the endothermicity of the reaction. Still greater entropy changes would occur in the formation of complexes between the anion of ethylenediaminetetra-acetic acid carrying four negative charges and, *e.g.*, rare-earth cations. Increase in the chain-length of the ligand may well produce only minor alterations in a large total entropy effect, so that ring-enlargement

FIG. 4. *The relation between the magnitude of the chelate effect and the stability of the reference ammonia complexes.*



might effect relatively small changes in the ' chelate effect ' such as appear for the replacement reactions oxalate/malonate, malonate/glutarate, etc., of Table 5. If the stability of Enta complexes of the alkaline-earth and transition metals is due predominantly to entropy increases on chelation, it should be possible to correlate these with the standard entropies of the ions concerned. If the entropy changes on replacing Enta by its homologue $(HO_2C{\cdot}CH_2)_2N{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}N(CH_2{\cdot}CO_2H)_2$ are negligible, the decreases in stability given in Table 2 must originate from differences in the heats of reaction which should depend upon specific properties such as the sum of the first and the second ionisation potential (Irving and Williams, *loc. cit.*). Thermochemical studies of both of these problems, which should contribute to a critical evaluation of Schwarzenbach's theory, are now in progress in these laboratories.

EXPERIMENTAL

Materials.—A commercial specimen of 1 : 3-diaminopropane (Messrs. Light & Co.) was refluxed over freshly fused and finely powdered barium oxide and fractionated, the fraction of b. p. 135—136°/760 mm. being collected in a weight-burette fitted with a " Sofnolite " guard tube. The purity, determined by titration of known amounts against standard hydrochloric acid, was never less than 98·5%. Glycine (a pure laboratory specimen), recrystallized several times from water, had m. p. 233° (decomp.). β-Alanine was prepared according to *Org. Synth.*, Coll. Vol. II, p. 19. After recrystallization it had m. p. 197° (decomp.). Both amino-acids were examined chromatographically and shown to be homogeneous.

" AnalaR " salts were used throughout and the apparatus and procedure for determining stability constants were substantially as previously described (Irving and Griffiths, *J.*, 1954, 213).

Acid Dissociation Constants of 1 : 3-*Diaminopropane.*—60 ml. of 0·1682M-hydrochloric acid, 25 ml. of 0·0666M-barium chloride, 11 ml. of 0·1M-potassium chloride, and 4 ml. of 1·605M-diamine solution in 0·1M-potassium chloride were transferred to the titration apparatus kept in a thermostat at 25° ± 0·05°, and the pH measured after successive additions of a 1·605M-solution of 1 : 3-diaminopropane in 0·1M-potassium chloride. The solution was stirred with a fine stream of nitrogen freed from carbon dioxide and equilibrated with water vapour. Steady potentials were obtained within 30 sec. The method of calculation was that described by Irving and Griffiths (*loc. cit.*).

Total vol. of diamine, ml.	pH	$\bar{n}_B$	pK (calc.)	Total vol. of diamine, ml.	pH	$\bar{n}_B$	pK (calc.)
4·00	8·83	1·571	8·97	12·2	10·70	0·553	10·72
4·16	8·93	1·511	8·97	12·36	10·72	0·5087	10·70
4·24	8·98	1·483	8·97	12·44	10·73	0·5055	10·71
4·32	9·025	1·455	8·97	12·52	10·74	0·5021	10·72
4·40	9·07	1·429	8·98	12·60	10·745	0·4999	10·72
4·48	9·11	1·404	8·975	12·68	10·75	0·4961	10·72
4·56	9·16	1·379	8·985	12·76	10·755	0·4927	10·72
4·64	9·20	1·355	8·99	12·84	10·76	0·4897	10·72
4·80	9·265	1·310	8·975	13·00	10·765	0·4838	10·72
	Average value of $pK_{BH_2}^{++}$		8·97(5)	13·20	10·78	0·4764	10·72
					Average value of pK_{BH}^{+}		10·72

Formation Curve for Copper and 1 : 3-*Diaminopropane.*—A mixture of 60·00 ml. of 0·1682M-hydrochloric acid, 25 ml. of 0·0499M-copper sulphate, 3·00 ml. of 1·605M-diaminopropane, and 12 ml. of 0·1M-potassium chloride was transferred to the titration vessel, and the pH measured after successive additions of a 1·605M-solution of the diamine in 0·1M-potassium chloride. Values of $\bar{n}$ and pB were calculated as previously described (Irving and Griffiths, *loc. cit.*). The results are plotted in Fig. 1.

Dissociation Constants of Amino-acids.—A mixture of 50 ml. of 0·1100M-hydrochloric acid and 50 ml. of 0·05M-glycine in 0·05M-sodium chloride was titrated with carbonate-free 1·085M-sodium hydroxide in the titration apparatus in a thermostat at 20° ± 0·05°. The pH was measured as soon as the potentials became steady. Similar measurements were carried out with β-alanine. The two sets of dissociation constants reported in Table 3 were obtained by an obvious extension of the methods reported for the aliphatic diamines (*loc. cit.*). In a series of measurements in which the ionic strength was varied by the addition of sodium chloride it was confirmed that such changes had very little effect on the magnitude of $pK_{ZH_2^{\pm}}$ but considerably influenced that of $pK_{ZH^{\pm}}$. Values obtained in the present work lay on a smooth curve when plotted against μ or $\sqrt{\mu}$ with data in the literature (for references, see Irving and Williams, *J.*, 1953, 3192), and in calculating stability constants of metal complexes (see below) the value appropriate to the ionic strength used was obtained by interpolation.

Stability Constants of Metal Complexes of Glycine and β-*Alanine.*—These were calculated from data obtained at 20° by titration, with carbonate-free 1·100N-sodium hydroxide, of 50 ml. of a mixture of 0·025M-metal sulphate, 0·05M-glycine, and 0·055M-hydrochloric acid. With β-alanine the concentration of metal had to be reduced to M/120 to avoid premature precipitation. Typical results for the titration of nickel and β-alanine were as follows :

Ml. of 1·153N-NaOH	pH	$\bar{n}$	pB	Ml. of 1·153N-NaOH	pH	n	pB	Ml. of 1·153N-NaOH	pH	n	pB
2·20	4·58	0·0	7·35	2·60	7·15	0·647	4·49	2·94	8·42	1·520	3·29
2·40	5·90	0·112	5·99	2·72	7·62	0·984	4·04	2·96	8·49	1·566	3·23
2·50	6·69	0·363	4·92	2·74	7·71	1·017	3·96	2·98	8·57	1·600	3·16
2·52	6·80	0·418	4·81	2·86	8·13	1·333	3·57	3·00	8·63	1·656	3·10
2·54	6·90	0·474	4·72	2·88	8·20	1·381	3·50	3·04	8·78	1·730	2·97
2·56	6·98	0·529	4·64	2·90	8·27	1·424	3·43	3·08	8·90	1·801	2·85
2·58	7·06	0·585	4·56	2·92	8·35	1·474	3·37				

During the titration the ionic strength fell from 0·088 to 0·078 and the value $pK_{ZH^{+}} = 10·26$ was used in the calculation of stability constants. With zinc the titration could only be carried up to $\bar{n} = 0·2$, so the value of log k_1 is very approximate.

Polarographic Measurements of Stability Constants.—Preliminary studies were carried out with a Tinsley recording polarograph but a manual instrument was used for the definitive measurements. The polarographic cell was kept in a thermostat at 25° ± 0·1°, and a normal calomel electrode was used with a saturated potassium chloride agar-agar bridge of low resistance. Plots of E versus $\log i/(i_{max.} - i)$ were drawn for every solution studied, the intercept giving $E_{\frac{1}{2}}$, the half-wave potential, and the slope the value of $0{\cdot}059/p$; measurements were rejected if this measured slope differed significantly from the theoretical value of 0·0295 for a bivalent ion. Solutions were made up by weight from " AnalaR " reagents, and 1 : 3-diaminopropane was freshly distilled over barium oxide immediately before use.

Typical results are shown below for a copper solution of strength 10^{-4}M where the ionic strength was kept at 0·1 by addition of potassium nitrate. The capillary characteristics were $m^{\frac{2}{3}}t^{\frac{1}{6}} = 0{\cdot}1432$ mg./sec., and 0·01% gelatin was present as a maximum suppressor. Three independent determinations of $E_{\frac{1}{2}}$ for 10^{-4}M-copper sulphate in 0·1M-potassium nitrate gave 0·0205, 0·0195, and 0·0199 v.

Concn. of 1 : 3-diaminopropane, [L], mole/l.	0	0·0194	0·0486	0·0973	0·1944	0·4860
Half-wave potential, $E_{\frac{1}{2}}$, v	0·2000	−0·3710	−0·3933	−0·4115	−0·4290	−0·4535

Plotted according to the equation

$$\Delta E_{\frac{1}{2}} = E_{\frac{1}{2}}\text{ (complex)} - E_{\frac{1}{2}}\text{ (simple)} = \frac{0{\cdot}059}{p}\log K_n - \frac{0{\cdot}059n}{p}\log [\mathrm{L}]$$

these results give a line of slope 0·0585, so, since $p = 2$ for Cu^{++}, n must be 2 and the complex present is $Cu(dmp)_2^{++}$. The intercept has the value 0·4915, whence $\log \beta_2 = 16{\cdot}67$ in satisfactory agreement with the potentiometric measurements.

Measurements with $1{\cdot}075 \times 10^{-3}$M-cadmium ions under the same conditions gave the following results :

Concn. of 1 : 3-diaminopropane, mole/l.	0	0·0608	0·1215	0·1823	0·2673	0·3645	0·6075	1·215
$-E_{\frac{1}{2}}$, v	0·5820	0·7363	0·7530	0·7613	0·7640	0·7810	0·8005	0·8260

When the half-wave potential is plotted against the decadic logarithm of the concentration of diamine a segmented curve results. At high concentrations the slope is $0{\cdot}086 = 0{\cdot}059n/2$ for the Cd^{++} ion, whence $n = 3$ and the predominant species must be the tris-complex $Cd(dmp)_3^{++}$. With lower concentrations of ligand the slope is 0·057, whence $n = 2$, showing that the bis-complex $Cd(dmp)_2^{++}$ is now the principal species. From the intercepts the values $\log_{10} \beta_2 = 7{\cdot}42$ and $\log_{10} \beta_3 = 8{\cdot}03$ are obtained for the respective over-all stability constants.

In order to determine the stability constants of β-alanine–copper complexes polarographically, values of $E_{\frac{1}{2}}$ were measured in a series of buffer solutions (prepared from 0·1M-sodium hydroxide and 0·1M-potassium dihydrogen phosphate) each of which was $4{\cdot}168 \times 10^{-4}$M with respect to cupric ion and 0·025M with respect to β-alanine. The ionic strength was adjusted to 0·1 in each case by addition of potassium nitrate, preliminary estimates of stability constants and measurements of pH enabling the correct amount to be arrived at by successive approximations. Typical results follow :

pH	8·05	8·82	9·26	9·72	10·23
$-\Delta E_{\frac{1}{2}}$, v	0·1515	0·1920	0·2150	0·2350	0·2550
[β-Alanine ion]/$[Cu^{2+}]$	0·4	1·7	4·5	11	25
$\log K_2$ (calc.)	12·96	12·81	12·69	12·58	12·61

The concentration of free amino-acid was calculated from the pH by using Henderson's equation and assuming the value $pK_{ZH^+} = 10{\cdot}36$ for the dissociation constant of the β-alanine zwitterion (May and Felsing, *J. Amer. Chem. Soc.*, 1951, **73**, 406). Values of $\log \beta_2$ calculated by the equation given previously are not constant because the ligand : metal ratio was too low in the less alkaline solutions. Omitting the results for pH 8·05 and 8·82, we obtain an average $\log \beta_2 = 12{\cdot}65$, in satisfactory agreement with the potentiometric measurements.

We are indebted to J. M. M. Griffiths for the potentiometric measurements with 1 : 3-diaminopropane, and to the Christopher Welch Fund for the purchase of a polarograph.

THE INORGANIC CHEMISTRY LABORATORY,
SOUTH PARKS ROAD, OXFORD.

[*Received, June 15th,* 1953.]

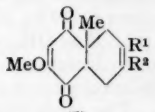
The Addition of Isoprene to 4-Methoxytoluquinone.

By W. A. Ayer, L. G. Humber, and W. I. Taylor.

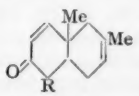
[Reprint Order No. 5356.]

The Diels–Alder addition of isoprene to 4-methoxytoluquinone affords *cis*-1 : 4 : 5 : 8 : 9 : 10-hexahydro-2-methoxy-6 : 10-dimethyl-1 : 4-dioxonaphthalene, whose constitution is proved by a series of reactions which lead to 1 : 6-dimethyl-2-naphthol. Syntheses of 1 : 6-dimethyl-, 1 : 4 : 6-trimethyl-, and 1 : 4 : 7-trimethyl-2-naphthols are recorded, and an error in the literature relating to the supposed synthesis of the latter is corrected.

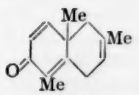
The chemistry of the adduct (I; $R^1 = R^2 = H$) formed by the Diels–Alder reaction between butadiene and 4-methoxytoluquinone has been extensively investigated by Woodward, Sondheimer, Taub, Heusler, and McLamore (*J. Amer. Chem. Soc.*, 1952, **74**, 4223). We have carried out the reaction between isoprene and 4-methoxytoluquinone as a model for the elaboration of sesquiterpenes of the eudalene class. The product, obtained in good yield, was (I; $R^1 = Me$; $R^2 = H$) and no trace of the desired adduct (I; $R^1 = H$; $R^2 = Me$) was observed.



(I)



(II)



(III)

The *cis*-adduct was isomerised to the *trans*-adduct after the method of Woodward *et al.* (*loc. cit.*), then reduced with lithium aluminium hydride; the product on treatment with sulphuric acid in dioxan afforded *trans*-1 : 2 : 5 : 8 : 9 : 10-hexahydro-6 : 10-dimethyl-2-oxo-1-naphthol (II; R = OH). This compound was converted *via* established procedures successively into the acetate (II; R = OAc), deacetoxy-product (II; R = H), formyl derivative (II; R = CHO), and finally *trans*-1 : 2 : 5 : 8 : 9 : 10-hexahydro-1 : 6 : 10-trimethyl-2-oxonaphthalene (II; R = Me), which on selenium dehydrogenation gave 1 : 6-dimethyl-2-naphthol.

For comparison a sample of the latter was synthesised from 6-bromo-2-methoxy-1-methylnaphthalene (Fries, *Ber.*, 1906, **39**, 442) *via* reaction of its Grignard derivative with methyl sulphate to form 2-methoxy-1 : 6-dimethylnaphthalene, followed by demethylation of the latter.

Reduction of (II; R = Me) in the presence of palladium on charcoal (uptake of 1 mol. of hydrogen) yielded *trans*-1 : 2 : 3 : 4 : 5 : 8 : 9 : 10-octahydro-1 : 6 : 10-trimethyl-2-oxonaphthalene, characterised as its yellow 2 : 4-dinitrophenylhydrazone. Attempts to prepare the dienone (III) from the unsaturated ketone (II; R = Me) by reaction with *N*-bromosuccinimide, pyridinium bromide perbromide, or selenium dioxide were unsuccessful and the only product which could be isolated was (II; R = H) in poor yield as its 2 : 4-dinitrophenylhydrazone.

Cocker, Fateen, and Lipman (*J.*, 1951, 926) have shown that methyl *p*-xylyl ether will condense with methylsuccinic anhydride in the presence of aluminium chloride in nitrobenzene or carbon disulphide to furnish β-(4-methoxy-2 : 5-dimethylbenzoyl)-α-methylpropionic acid (the α-isomer) but they were not able to isolate the β-isomer [β-(4-methoxy-2 : 5-dimethylbenzoyl)-β-methylpropionic acid]. However, we have been able to prepare in tetrachloroethane the β-isomer which was separated from a much larger quantity of the α-isomer by fractional crystallisation. Elaboration of these compounds into the required 1 : 4 : 6-trimethyl- and 1 : 4 : 7-trimethyl-2-naphthols was carried out by classical methods. We point out, however, that in the course of this work it appears that the compounds described by Cocker *et al.* (*loc. cit.*) as 5 : 6 : 7 : 8-tetrahydro-1 : 4 : 7-trimethyl-8-oxo-2-naphthol, 5 : 6 : 7 : 8-tetrahydro-1 : 4 : 7-trimethyl-2-naphthol, and 1 : 4 : 7-trimethyl-2-naphthol are in reality the corresponding methyl ethers. This error has arisen because

Cocker *et al.* (*loc. cit.*) assumed with some justification (see *e.g.* an earlier paper by these workers, *J.*, 1950, 1781) that demethylation has occurred during the cyclisation of the (+)-isomer to the tetralone in 80% sulphuric acid.

Experimental

1 : 4 : 5 : 8 : 9 : 10-*Hexahydro*-2-*methoxy*-6 : 10-*dimethyl*-1 : 4-*dioxonaphthalene* (I; R^1 = Me, R^2 = H).—4-Methoxytoluquinone (71·5 g.), isoprene (105 g.), benzene (200 c.c.), and a trace of quinol were heated at 90—100° in a sealed tube for 6 days, then filtered through glass wool, and concentrated to a small volume. Addition of light petroleum (b. p. 60—80°; 250 c.c.) gave the crude cis-*diketone* (87·9 g.), m. p. 115—118° (from light petroleum) (Found: C, 71·0; H, 7·3. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). Reduction of the *cis*-diketone (1·4 g.) with lithium aluminium hydride in tetrahydrofuran afforded the pure cis-*glycol* (0·4 g.), m. p. 130—132° (from benzene) (Found: C, 69·6; H, 8·9. $C_{13}H_{20}O_3$ requires C, 69·6; H, 9·0%).

trans-1 : 4 : 5 : 8 : 9 : 10-*Hexahydro*-2-*methoxy*-6 : 10-*dimethyl*-1 : 4-*dioxonaphthalene*.—A solution of sodium dithionite (1·9 g.) in N-sodium hydroxide (12·5 c.c.) was added dropwise under nitrogen to the *cis*-diketone (10 g.) and sodium dithionite (0·6 g.) in dioxan (20 c.c.) at 70°. N-Sodium hydroxide was then added until all the solid disappeared. The solution was inoculated with a small quantity of powdered *trans*-diketone (obtained in small scale preliminary experiments), then diluted with water (250 c.c.), acidified with N-hydrochloric acid, and cooled in ice. The precipitated trans-*diketone* (6·3 g.) was filtered off and crystallised from methanol to m. p. 127—128° (Found: C, 70·8, 70·8; H, 7·4, 7·4. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%).

trans-1 : 2 : 5 : 8 : 9 : 10-*Hexahydro*-6 : 10-*dimethyl*-2-*oxo*-1-*naphthol* (II; R = OH).—Reduction of *trans*-diketone (10 g.) with lithium aluminium hydride in tetrahydrofuran afforded a crude oily *trans*-glycol (3·9 g.) which yielded pure *trans*-1 : 4 : 5 : 8 : 9 : 10-hexahydro-2-methoxy-6 : 10-dimethylnaphthalene-1 : 4-diol, m. p. 164—165° (from benzene). The crude *trans*-glycol (2 g.) and 2N-sulphuric acid (9 c.c.) in dioxan (11 c.c.) were kept at room temperature for 24 hr., then extracted with ether, to furnish the trans-*ketol* (0·54 g.), m. p. 58° [from light petroleum (b. p. 60—80°)] (Found: C, 74·5; H, 8·4. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·4%). The *acetate* (II; R = OAc) had m. p. 60° (from light petroleum) (Found: C, 71·7; H, 7·7. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%).

trans-1 : 2 : 5 : 8 : 9 : 10-*Hexahydro*-6 : 10-*dimethyl*-2-*oxonaphthalene* (II; R = H).—Zinc dust (112 g.) was added to a vigorously stirred refluxing solution of the acetate (13·1 g.) in acetic anhydride (112 c.c.). After 10 min. the zinc was filtered off and the acetic anhydride removed *in vacuo* through a Vigreux column. An ethereal solution of the residue was washed successively with dilute sulphuric acid, sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), and then concentrated. Distillation of the residue (9·4 g.) furnished the trans-*ketone* (5·2 g.), b. p. 79—83°/0·1 mm. (Found: C, 81·3; H, 9·3. $C_{12}H_{16}O$ requires C, 81·8; H, 9·2%).

trans-1 : 2 : 5 : 8 : 9 : 10-*Hexahydro*-6 : 10-*dimethyl*-6-*oxo*-1-*naphthaldehyde* (II; R = CHO).—Ethyl formate (21 c.c.) was added to a well-stirred suspension of sodium methoxide (7 g.) in dry benzene (45 c.c.) under nitrogen followed by the dropwise addition of the *trans*-ketone (9·5 g.) in benzene (45 c.c.) during 1 hr. at 0°. After dilution of the mixture with benzene (40 c.c.) stirring was continued for a further 20 hr. at room temperature. The solution was washed with ice-cold sulphuric acid, then extracted with cold 0·3N-potassium hydroxide. Acidification of the alkaline extract afforded an oil. A solution of this in ether–benzene (1 : 1) was washed with water, dried (Na_2SO_4), and concentrated *in vacuo* to yield the crude *aldehyde* (7·7 g.). (For analysis, a sample was distilled at 95—100°/0·05 mm. Found: C, 76·5; H, 7·9. $C_{13}H_{16}O_3$ requires C, 76·5; H, 7·9%.) The absorption spectrum in ethanol showed maxima at 240 and 312 mμ; ε = 6600 and 3500, respectively.

trans-1 : 2 : 5 : 8 : 9 : 10-*Hexahydro*-1 : 6 : 10-*trimethyl*-2-*oxonaphthalene* (II; R = Me).—The aldehyde (7·5 g.), sodium ethoxide (3 g.), and methyl iodide (6 g.) were refluxed for 3 hr. in absolute ethanol (30 c.c.). The solution was concentrated, and a solution of the residue in ether washed with water and concentrated. The residue (6·8 g.) distilled to furnish crude *trans*-1 : 2 : 5 : 8 : 9 : 10-hexahydro-1 : 6 : 10-trimethyl-2-oxo-1-naphthaldehyde (5·1 g.), b. p. 65—110°/0·1 mm. (light absorption: max. 228 mμ; ε = 12,000 in EtOH). The crude methylated derivative (5·1 g.) in dioxan (230 c.c.) was set aside with ice-cold potassium hydroxide (6·5 g.) in water (230 c.c.) for 3 hr., then saturated with salt, and extracted with ether. After concentration and distillation pure trans-1 : 2 : 5 : 8 : 9 : 10-*hexahydro*-1 : 6 : 10-*trimethyl*-2-*oxonaphthalene* (2·4 g.) was obtained, b. p. 60—70°/0·1 mm. (Found: C, 81·6; H, 9·3. $C_{13}H_{18}O$ requires C, 82·1; H, 9·6%). The absorption spectrum measured in ethanol showed a maximum

at 226 mμ (ε = 12,100). The 2 : 4-*dinitrophenylhydrazone* had m. p. 165—166° (from *n*-butanol) (Found : C, 61·0; H, 5·6. $C_{19}H_{22}O_4N_4$ requires C, 61·6; H, 6·0%).

trans-1 : 2 : 3 : 4 : 5 : 8 : 9 : 10-*Octahydro*-1 : 6 : 10-*trimethyl*-2-*oxonaphthalene*.—The *trans*-hexahydro-compound (50 mg.) in ethanol took up 1 mol. of hydrogen in 10 min. in the presence of palladium on charcoal (50 mg.). The catalyst was filtered off and the resulting solution treated with an ethanolic solution of 2 : 4-dinitrophenylhydrazine hydrochloride, yielding the 2 : 4-dinitrophenylhydrazone (61 mg.) of the *trans*-octahydronaphthalene as yellow crystals (from *n*-butanol), m. p. 164—166° (Found : N, 16·2. Calc. for $C_{19}H_{24}O_4N_4$: N, 15·0%).

1 : 6-*Dimethyl*-2-*naphthol*.—The *trans*-ketone (II; R = Me; 0·5 g.) was heated for 10 hr. with selenium (1 g.) at 300—330°, and the mixture then cooled, powdered, and exhaustively extracted with chloroform, from which the phenolic portion was isolated with 5% sodium hydroxide. Sublimation at 50—60°/0·1 mm. yielded the crude solid phenol (81 mg.) which after several crystallisations from light petroleum (b. p. 60—80°) afforded pure 1 : 6-dimethyl-2-naphthol, m. p. 106—107° (Found : C, 83·8; H, 7·2. Calc. for $C_{12}H_{12}O$: C, 83·7; H, 7·0%).

The Grignard derivative of 6-bromo-2-methoxy-1-methylnaphthalene (1·5 g.) was prepared by refluxing it in dry ether (75 c.c.) with magnesium turnings (0·3 g.) in an atmosphere of dry nitrogen. After all the magnesium had dissolved methyl sulphate (1·8 g.) in ether (50 c.c.) was added and the mixture refluxed for a further hour, set aside at room temperature overnight, then decomposed with dilute hydrochloric acid. The ethereal extract was concentrated, yielding crude 2-methoxy-1 : 6-dimethylnaphthalene (1·3 g.). A mixture of this compound (0·5 g.), 48% hydrobromic acid (20 c.c.), and acetic acid (4 c.c.) was refluxed for 4 hr., then diluted with water, and extracted with ether. Extraction of the ethereal solution with 5% sodium hydroxide afforded the crude naphthol (80 mg.) which was crystallised to constant m. p. 105—106° from light petroleum (b. p. 60—80°) (Found : C, 83·6; H, 6·9%). There was no depression of m. p. on admixture with the sample synthesised by the route described above.

1 : 4 : 7-*Trimethyl*-2-*naphthol*.—β-(4-*Methoxy*-2 : 5-*dimethylbenzoyl*)-α-*methylpropionic acid*. Methyl *p*-xylyl ether (27·2 g.) was condensed with methylsuccinic anhydride (24 g.) by the use of aluminium chloride (67 g.) in nitrobenzene (200 c.c.). The crude acid (40 g.) was crystallised from aqueous ethanol to constant m. p. 151—152° (lit. 140°) (Found, in a sublimed sample : C, 66·9; H, 7·3. Calc. for $C_{14}H_{18}O_4$: C, 67·2; H, 7·3%). The semicarbazone (from aqueous ethanol) had m. p. 174—175° (lit. 166°) (Found : N, 13·2. Calc. for $C_{15}H_{21}O_4N_3$: N, 13·6%).

γ-(4-*Methoxy*-2 : 5-*dimethylphenyl*)-α-*methylbutyric acid*. The keto-acid (37 g.) was reduced by amalgamated zinc to the required butyric acid (22·5 g.), m. p. 100—101° (from aqueous ethanol) (lit. 89—90°) (Found : C, 70·5; H, 8·7. Calc. for $C_{12}H_{20}O_3$: C, 71·2; H, 8·5%).

1 : 2 : 3 : 4-*Tetrahydro*-7-*methoxy*-2 : 5 : 8-*trimethylnaphthalene*. The butyric acid (9 g.) was heated with concentrated sulphuric acid at 70° for 10 min. and yielded the methoxy-tetralone (6·5 g.), m. p. 71—72° (from benzene–light petroleum) (Found : C, 77·1; H, 8·7; OMe, 14·2. Calc. for $C_{14}H_{18}O_2$: C, 77·0; H, 8·3; OMe, 14·2%). Cocker *et al.* (*loc. cit.*) recorded m. p. 75° for their " hydroxy-tetralone."

5 : 6 : 7 : 8-*Tetrahydro*-1 : 4 : 7-*trimethyl*-8-*oxo*-2-*naphthol*. The foregoing ketone (5·3 g.), refluxed with 47% hydrobromic acid (65 c.c.) for 3 hr., furnished the *hydroxy-tetralone* (4·5 g.), m. p. 151° (from benzene–light petroleum) (Found : C, 76·3; H, 8·1. $C_{13}H_{16}O_2$ requires C, 76·4; H, 7·9%).

5 : 6 : 7 : 8-*Tetrahydro*-1 : 4 : 7-*trimethyl*-2-*naphthol*. The hydroxy-tetralone (1·17 g.) was reduced by amalgamated zinc to the required *hydroxy-tetralin* (550 mg.), m. p. 99—100° (from aqueous ethanol) (Found : C, 81·9; H, 9·5. $C_{13}H_{18}O$ requires C, 82·0; H, 9·5%). Methylation with methyl sulphate and alkali yielded the methoxy-tetralin, m. p. 29° (Found : OMe, 14·5. Calc. for $C_{14}H_{20}O$: OMe, 14·2%). Cocker *et al.* (*loc. cit.*) record m. p. 32° for their " hydroxytetralin."

1 : 4 : 7-*Trimethyl*-2-*naphthol*. The hydroxy-tetralin (250 mg.) was heated with selenium (700 mg.) at 330—350° for 1 hr. and yielded the *naphthol* (110 mg.) which was extracted from the mixture with methanol and crystallised from aqueous ethanol; it had m. p. 141—142° (Found : C, 83·8; H, 7·6. $C_{13}H_{14}O$ requires C, 83·8; H, 7·6%). Light absorption : max., 240, 275, 290, 300, 335 mμ; log ε = 4·70, 3·50, 3·71, 3·62, 3·22, respectively in ethanol.

1 : 4 : 6-*Trimethyl*-2-*naphthol*.—1 : 2 : 3 : 4-*Tetrahydro*-7-*methoxy*-3 : 5 : 8-*trimethyl*-1-*oxonaphthalene*. Methyl *p*-xylyl ether (27·2 g.) was condensed with methylsuccinic anhydride (24 g.) by use of aluminium chloride (67 g.) in tetrachloroethane. The crude acids were fractionally crystallised from aqueous ethanol, furnishing pure β-(4-methoxy-2 : 5-dimethylbenzoyl)-β-methylpropionic acid (7·2 g.), m. p. 89—91°, which did not form a semicarbazone. Reduction of the acid with amalgamated zinc gave the oily γ-phenylbutyric acid (5·2 g.), which was heated

directly in concentrated sulphuric acid at 70° for 10 min. to yield 1 : 2 : 3 : 4-*tetrahydro*-7-*methoxy*-3 : 5 : 8-*trimethyl*-1-*oxonaphthalene* (1·6 g.), m. p. 74° (from benzene–light petroleum) (Found: C, 77·1; H, 8·3; OMe, 11·9. $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3; OMe, 14·2%).

5 : 6 : 7 : 8-*Tetrahydro*-1 : 4 : 6-*trimethyl*-8-*oxo*-2-*naphthol*. The foregoing ketone (1·6 g.), refluxed with hydrobromic acid, gave the *hydroxy-tetralone* (550 mg.), m. p. 176° (from aqueous ethanol) (Found: C, 76·1; H, 8·1. $C_{13}H_{16}O_2$ requires C, 76·4; H, 7·9%).

5 : 6 : 7 : 8-*Tetrahydro*-1 : 4 : 6-*trimethyl*-2-*naphthol*. The hydroxy-tetralone (550 mg.) was reduced by amalgamated zinc to the required *hydroxy-tetralin* (360 mg.), m. p. 106—107° (from benzene–light petroleum) (Found: C, 82·0; H, 9·5. $C_{13}H_{18}O$ requires C, 82·0; H, 9·5%).

1 : 4 : 6-*Trimethyl*-2-*naphthol*. The tetrahydronaphthol (160 mg.) was heated with selenium, yielding the *naphthol* (72 mg.), m. p. 116—117° (from aqueous ethanol) (Found: C, 83·4; H, 8·4. $C_{13}H_{14}O$ requires C, 83·8; H, 7·6%). Light absorption in ethanol: max., 235, 285, 340 mμ; $\log \varepsilon = 4{\cdot}59$, 3·50, 3·16, respectively.

We are indebted to the National Research Council of Canada for a grant and a N.R.C. bursary to one of us (W. A. A.).

THE UNIVERSITY OF NEW BRUNSWICK. [*Received, May 5th*, 1954.]

The Thermal Decomposition of Octyl Nitrite in Hydrocarbon Solvents.

By BERNARD A. GINGRAS and WILLIAM A. WATERS.

[Reprint Order No. 5406.]

The thermal decomposition of octyl nitrite in solution gives rise to nitric oxide and octyloxy-radicals. The latter abstract hydrogen from the solvents, giving octyl alcohol and hydrocarbon radicals which are easily oxidised to the corresponding aldehydes or ketones. Both the nitric oxide and products derived from these hydrocarbon radicals have been characterised by combination with 2-cyano-2-propyl (1-cyano-1-methylethyl) radicals: thus the decomposition in toluene has given, amongst other products, *N*-benzyl-*ON*-di-(2-cyano-2-propyl)hydroxylamine, the obvious precursor of which is α-nitroso-toluene.

THE vapour-phase pyrolysis of alkyl nitrites at 170—240°, which can be represented as

$$2R{\cdot}CH_2{\cdot}O{\cdot}NO \longrightarrow R{\cdot}CHO + R{\cdot}CH_2{\cdot}OH + 2NO$$

(Steacie, "Atomic and Free Radical Reactions," pp. 141—143, Reinhold Publ. Corp., New York, 1946) can be explained (Rice and Rodowskas, *J. Amer. Chem. Soc.*, 1935, **57**, 350) by the mechanism

$$R{\cdot}CH_2{\cdot}O{\cdot}NO \longrightarrow R{\cdot}CH_2{\cdot}O{\cdot} + NO \ (E = 37 \pm 1 \text{ kcal.}) \quad . \ . \ . \quad (1)$$

$$R{\cdot}CH_2{\cdot}O{\cdot} + R{\cdot}CH_2{\cdot}O{\cdot}NO \longrightarrow R{\cdot}CH_2{\cdot}OH + R{\cdot}\dot{C}H{\cdot}O{\cdot}NO \quad . \ . \ . \ . \ . \ . \quad (2)$$

$$R{\cdot}\dot{C}H{\cdot}O{\cdot}NO \longrightarrow R{\cdot}CHO + NO \quad . \ . \ . \ . \ . \ . \ . \ . \ . \ . \quad (3)$$

though (1) is reversible and (4) is a possible alternative to (2) and (3) (Levy, *ibid.*, 1953, **75**, 1801).

$$2R{\cdot}CH_2{\cdot}O{\cdot} \longrightarrow R{\cdot}CHO + R{\cdot}CH_2{\cdot}OH \quad . \ . \ . \ . \ . \ . \ . \ . \quad (4)$$

Vapour-phase photolysis, which appears not to give alcohols (Thomson and Purkis, *Trans. Faraday Soc.*, 1936, **32**, 1466; Thomson and Dainton, *ibid.*, 1937, **33**, 1546), has been represented as giving molecular decomposition products and not free radicals,

e.g., $$R{\cdot}CH_2{\cdot}O{\cdot}NO \longrightarrow R{\cdot}CHO + HNO \quad . \ . \ . \ . \ . \ . \ . \ . \ . \ . \quad (5)$$

and $$Me_3C{\cdot}O{\cdot}NO \longrightarrow Me_2CO + Me{\cdot}NO \quad . \ . \ . \ . \ . \ . \ . \ . \ . \ . \quad (6)$$

(Coe and Doumani, *J. Amer. Chem. Soc.*, 1948, **70**, 1516).

Rice and Rodowskas's mechanism (*loc. cit.*) has received strong support from Kornblum and Oliveto (*ibid.*, **1949**, **71**, 226) who examined the pyrolysis of optically active liquid (+)-2-octyl nitrite at 100° and isolated nitric oxide, octan-2-one, and active (+)-octan-2-ol, thus demonstrating that the asymmetric free radical (I) picks up hydrogen without any rearrangement to (II).

(I) $C_6H_{13}-\underset{H}{\overset{CH_3}{C}}-O\cdot$ $\qquad$ $C_6H_{13}-\underset{\cdot}{\overset{CH_3}{C}}-O-H$ (II)

Since the evidence for the presence of transient alkyloxy-radicals in pyrolyses of alkyl nitrites depends wholly on the validity of the reaction mechanism, we have attempted to demonstrate the formation of *n*-octyloxy-radicals, $C_7H_{15}\cdot CH_2\cdot O\cdot$, from octyl nitrite by carrying out its decomposition in hydrocarbon solvents in the presence of decomposing αα′-azo*iso*butyronitrile, hoping that the reaction (7) might occur sufficiently to allow us to isolate the diagnostic radical combination product. This aim has not been achieved, for the octyloxy-radicals abstract hydrogen from the solvents used, giving hydrocarbon radicals from which typical derivatives have been isolated.

$$C_8H_{17}\cdot O\cdot + \cdot CMe_2\cdot CN \longrightarrow C_8H_{17}\cdot O\cdot CMe_2\cdot CN \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

The slow thermal decomposition of octyl nitrite in boiling toluene containing αα′-azo*iso*butyronitrile gave octyl alcohol, benzaldehyde, *ONN*-tri-(2-cyano-2-propyl)hydroxylamine (the addition product of nitric oxide and 2-cyano-2-propyl radicals; Gingras and Waters, *J.*, **1954**, 1920), and *N*-benzyl-*ON*-di-(2-cyano-2-propyl)hydroxylamine (IV). Consequently the following reactions must have occurred :

$$C_8H_{17}\cdot O\cdot NO \longrightarrow C_8H_{17}\cdot O\cdot + NO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad [i.e.\ (1)]$$

$$NO + 3\dot{C}Me_2\cdot CN \longrightarrow (Me_2C\cdot CN)_2N\cdot O\cdot CMe_2\cdot CN \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

$$C_8H_{17}\cdot O\cdot + Ph\cdot CH_3 \longrightarrow C_8H_{17}\cdot OH + Ph\cdot CH_2\cdot \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

$$Ph\cdot CH_2\cdot + NO \longrightarrow Ph\cdot CH_2\cdot NO\ (III) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

$$Ph\cdot CH_2\cdot NO + 2\dot{C}Me_2\cdot CN \longrightarrow Ph\cdot CH_2\cdot N(CMe_2\cdot CN)\cdot O\cdot CMe_2\cdot CN\ (IV) \quad . \quad . \quad . \quad (11)$$

α-Nitrosotoluene (III) has never yet been prepared, but it evidently exists in boiling toluene solution, without rearranging to benzaldoxime, for a sufficient time to combine with two cyanopropyl radicals to give the tertiary hydroxylamine (IV) which has a very similar infra-red spectrum to those of the related tertiary hydroxylamines previously prepared by us from aromatic nitroso-compounds (Gingras and Waters, *loc. cit.*). Reduction of (IV) with zinc dust and acetic acid gave an amide, probably $Ph\cdot CH_2\cdot N(OH)\cdot CMe_2\cdot CO\cdot NH_2$, having an infra-red spectrum indicative of a secondary hydroxylamine.

Benzaldehyde, but not octaldehyde, was also identified as a product of the decomposition of octyl nitrite in boiling toluene under carbon dioxide in the absence of αα′-azo*iso*butyronitrile. Neither dibenzyl nor 2-cyano-2-methyl-1-phenylpropane, $Ph\cdot CH_2\cdot CMe_2\cdot CN$, could be isolated, so that the combination of benzyl radicals with nitric oxide to give (III) must be a very fast reaction.

In the above reaction only a small percentage of the free 2-cyano-2-propyl radicals combine with the nitric oxide or α-nitrosotoluene, for the usual radical dimer, tetramethylsuccinonitrile, was a major reaction product. The trimer, 2 : 3 : 5-tricyano-2 : 3 : 5-trimethylhexane (Bickel and Waters, *Rec. Trav. chim.*, 1950, **69**, 1490), was also formed, and in addition a trace of a new isomeric dimer, 2 : 4-dicyano-2-methylpentane $NC\cdot CMe_2\cdot CH_2\cdot CHMe\cdot CN$ (V), was isolated. Bickel and Waters (*ibid.*, p. 312) had isolated the corresponding dimethyl ester in 15% yield from the decomposition of dimethyl αα′-azo*iso*butyrate and had suggested that the expected yield of the dimer (V) from αα′-azo*iso*butyronitrile would be less than 0·5% : slightly less than this has been isolated.

The reaction in boiling ethylbenzene proceeded somewhat differently, for resulting products, apart from dimers and trimer of 2-cyano-2-propyl radicals, were octyl alcohol,

acetophenone, and 2 : 5-dicyano-2 : 5-dimethyl-3-phenylhexane (VI), which had previously been prepared in this laboratory by Dr. A. F. Bickel from the direct reaction of αα′-azo-*iso*butyronitrile with styrene. The following reaction sequence may be postulated :

$$Ph\cdot CH_2\cdot CH_3 + C_8H_{17}\cdot O\cdot \longrightarrow Ph\cdot \dot{C}H\cdot CH_3 + C_8H_{17}\cdot OH \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

$$Ph\cdot \dot{C}H\cdot CH_3 + C_8H_{17}\cdot O\cdot \longrightarrow Ph\cdot CH{:}CH_2 + C_8H_{17}\cdot OH \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

or $$2Ph\cdot \dot{C}H\cdot CH_3 \longrightarrow Ph\cdot CH{:}CH_2 + Ph\cdot CH_2\cdot CH_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

$$Ph\cdot CH{:}CH_2 + 2\cdot CMe_2\cdot CN \longrightarrow NC\cdot CMe_2\cdot CHPh\cdot CH_2\cdot CMe_2\cdot CN \text{ (VI)} \quad . \quad . \quad . \quad (15)$$

Acetophenone was also produced in the absence of αα′-azo*iso*butyronitrile.

The reaction in boiling *iso*propylbenzene gave a very small yield of a white compound which appears to be 2-cyano-2-methyl-4-nitro-4-phenylpentane: this could possibly be formed by successive additions of nitric oxide and 2-cyano-2-propyl radicals to α-methylstyrene. Decompositions in diphenylmethane and in 1-methylnaphthalene gave octyl alcohol and respectively benzophenone and 1-naphthaldehyde but no significant amounts of other products.

Experimental

Freshly prepared *n*-octyl nitrite was used throughout: material which had been kept for 2 weeks had to be rejected since it contained aldehyde.

Reaction in Toluene.—(*a*) A solution of octyl nitrite (45 g., 0·28 mole) in toluene (50 ml.) containing a little αα′-azo*iso*butyronitrile (0·5 g.) was heated slowly to boiling and as soon as nitrous fumes were evolved a solution of αα′-azo*iso*butyronitrile (45 g., 0·28 mole) in toluene (1 l.) was added dropwise during 24 hr. A few drops of the reaction mixture when treated with 2 : 4-dinitrophenylhydrazine gave benzaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 233°. After distillation of the toluene the remaining liquid was distilled in steam. The aqueous layer of the distillate, on cooling, gave tetramethylsuccinonitrile (20 g.); light petroleum (b. p. 40—60°) precipitated a further 5 g. of this from the other layer (total recovery 67%). The petroleum solution on distillation gave octyl nitrite (b. p. 64°/20 mm.; 9 g., 20%) and octyl alcohol (b. p. 89°/20 mm.; 16 g., 54%): benzaldehyde and more tetramethylsuccinonitrile remained in higher-boiling residues. The organic material which had not distilled in steam was collected (7·7 g.) and chromatographed through an alumina column, giving first an oil, then the radical trimer (2 : 3 : 5-tricyano-2 : 3 : 5-trimethylhexane) (1·4 g.; m. p. and mixed m. p. 81°) and a few mg. of the new dimer (V), 2 : 4-*dicyano-2-methylpentane*, which, crystallised from aqueous alcohol, had m. p. 152—153° (Found: C, 70·8; H, 8·3; N, 21·2. $C_8H_{12}N_2$ requires C, 70·5; H, 8·8; N, 20·6%). Its infra-red spectrum was almost identical with that of tetramethylsuccinonitrile, with typical absorption bands at 4·49 μ (CN) and 7·23 and 7·30 μ (Me_2C group). When the oil was carefully fractionated through two more columns in succession there were obtained N-*benzyl*-ON-*ai*-(2-*cyano*-2-*propyl*)*hydroxylamine* (IV) (2 g.), which after crystallisation from light petroleum (b. p. 40—60°) had m. p. 58·5° (Found: C, 70·0; H, 7·5; N, 16·4. $C_{15}H_{19}ON_3$ requires C, 70·0; H, 7·4; N, 16·4%), and *ONN*-tri-(2-cyano-2-propyl)hydroxylamine (1·1 g.), m. p. and mixed m. p. 78°. Both compounds gave infra-red spectra showing the presence of CN and Me_2C groups and had similar absorptions in the 8—9μ region; the former also showed the strong band at 14·37 μ characteristic of a phenyl group. The nitrile (IV) (0·3 g.) in boiling acetic acid (10 ml.) was reduced by adding zinc dust (0·3 g.) in portions during 1 hr. After refluxing for a further 5 hr. the hot mixture was filtered, cooled, made alkaline, and extracted with ether. Chromatography of the extract gave a few mg. of N-*benzyl*-N-iso*butyramidohydroxylamine* which when crystallised from ether–light petroleum had m. p. 102°, and infra-red absorption bands at 2·95 μ (*s*, OH), 3·05 and 3·16 μ (*m*, NH), 6·00 and 6·18 μ (*m*, amide CO), 7·28 (*w*) and 7·34 μ(*m*) (Me_2C) and 14·29 μ (C_6H_5) (Found: C, 63·4; H, 7·7; N, 13·5. $C_{11}H_{16}O_2N_2$ requires C, 63·5; H, 7·7; N, 13·45%).

(*b*) Octyl nitrite (15 ml.) in toluene (100 ml.) was refluxed for 24 hr. in a rapid stream of carbon dioxide from a cylinder. After that time a few drops of the solution were sufficient to give an identifiable amount of benzaldehyde dinitrophenylhydrazone. The liquid on distillation yielded octyl alcohol (12·5 ml.) but no crystalline products could be isolated from the high-boiling residue.

Reaction in Ethylbenzene.—(*a*) αα′-Azo*iso*butyronitrile (16·4 g.) in ethylbenzene (1 l.) was added dropwise during 24 hr. to a gently refluxing solution of octyl nitrite (16 g.) in the same

solvent (50 ml.): all the nitrite had then decomposed. 1 ml. of the solution sufficed to give acetophenone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 235°. Tetramethylsuccinonitrile (46%) and octyl alcohol (70%) were isolated by steam-distillation (as above) and the residue (9·3 g.) was chromatographically separated into the trimer (0·9 g.; m. p. and mixed m. p. 81°), and 2 : 5-dicyano-2 : 5-dimethyl-3-phenylhexane (1·04 g., m. p. 121—122°), which proved to be identical with a specimen previously prepared in this laboratory by Dr. A. F. Bickel from αα′-azo*iso*butyronitrile and styrene (Found: C, 79·3; H, 8·0; N, 12·3. $C_{15}H_{20}N_2$ requires C, 79·0; H, 8·7; N, 12·3%). The specimens had identical infra-red spectra showing bands at 4·5 μ (CN), 7·20 and 7·31 μ (Me_2C), and 14·29 μ (C_6H_5).

(*b*) Carbon dioxide from a cylinder was passed for 24 hr. through a gently boiling solution of octyl nitrite (15 ml.) in ethylbenzene (100 ml.). After this time acetophenone 2 : 4-dinitrophenylhydrazone was obtained from a few drops of the reaction mixture: no crystalline products could be obtained from the high-boiling residue after fractionation.

Reaction in iso*Propylbenzene.*—αα′-Azo*iso*butyronitrile (10 g.) and octyl nitrite (10·5 ml.), dissolved in *iso*propylbenzene (600 ml.), were added dropwise during 6·5 hr. to a gently refluxing mixture of octyl nitrite (10 ml.) and *iso*propylbenzene. After steam-distillation the residue (8 g.) was chromatographically separated into the 2-cyano-2-propyl radical trimer, m. p. and mixed m. p. 81°, and *2-cyano-2-methyl-4-nitro-4-phenylpentane* (0·97 g.), which after crystallisation from light petroleum (b. p. 40—60°) had m. p. 67° (Found: C, 67·0; H, 6·9; N, 12·2. $C_{13}H_{16}O_2N_2$ requires C, 67·2; H, 6·9; N, 12·1%). Its infra-red spectrum showed absorption bands at 4·50 μ (CN), 7·22 and 7·33 μ (Me_2C), 14·28 μ (C_6H_5), and also strong bands at 6·53 and 7·38 μ indicative of a NO_2 group.

Reaction in Diphenylmethane.—Octyl nitrite (10 ml.) and diphenylmethane (50 g.) were heated for 6 hr. in an oil-bath at 155—160° during which time αα′-azo*iso*butyronitrile (7·25 g.) was added in small portions. Benzophenone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 238°, was obtained from a few drops of the resulting liquid. After distillation under reduced pressure and then steam-distillation the residue (9·3 g.) was chromatographed, and there were obtained the radical trimer (m. p. 81°) and benzophenone (*ca.* 5 g., b. p. 140°/10 mm. Found: C, 85·4; H, 5·8. Calc. for $C_{13}H_{10}O$: C, 85·7; H, 5·5%). Benzophenone 2 : 4-dinitrophenylhydrazone was also obtained when αα′-azo*iso*butyronitrile was not used.

Reaction in α-Methylnaphthalene.—This was carried out at 160° by the procedure used for *iso*propylbenzene. A few drops of the resulting solution then gave α-naphthaldehyde 2 : 4-dinitrophenylhydrazone, m. p. 254—255° (Found: C, 61·2; H, 3·8; N, 16·6. Calc. for $C_{17}H_{12}O_4N_4$: C, 60·7; H, 3·6; N, 16·7%); Coles and Dodds (*J. Amer. Chem. Soc.*, 1938, **60**, 853) record m. p. 254°. The residue after steam-distillation gave the radical trimer, m. p. 81°, but no other crystalline product.

One of us (B. A. G.) thanks the Merck Co. Ltd., Montreal, for a Canadian Post-Doctorate Overseas Fellowship held during the year 1953—1954.

The Dyson Perrins Laboratory, Oxford. [*Received, May 24th*, 1954.]

Nitryl Fluoride as a Nitrating Agent.

By G. Hetherington and P. L. Robinson.

[Reprint Order No. 5417.]

Nitryl fluoride is shown to be an active nitrating agent, and its behaviour with typical organic compounds is described. It is somewhat selective in its attack, leaving such deactivated aromatic compounds as nitrobenzene, benzoic acid, and benzaldehyde largely unchanged. With substances of intermediate reactivity nitration is rapid and smooth : the products are those which would result from the use of mixed acids. Highly reactive materials like aniline, anisole, and quinoline are converted immediately into intractable tars. These results are compared with those obtained when nitryl chloride is used.

Moissan and Lebeau (*Compt. rend.*, 1905, **140**, 1573, 1621), using material which probably contained some nitryl fluoride (see *J.*, 1954, 1119), obtained evidence of formation of ethyl nitrate from alcohol, of nitrobenzene from benzene, and of unspecified reactions with ether, chloroform, and turpentine. Using pure nitryl fluoride, now readily prepared, we have made a general survey of its nitrating properties by treating organic compounds, either alone or dissolved in an inert liquid. The materials and Pyrex vessels employed were dry (but not intensively dried) and the experiments were carried out without exposure to air. The results are recorded in a Table which gives, for convenience of comparison, the products obtained by Price and Sears (*J. Amer. Chem. Soc.*, 1953, **75**, 3276) in their experiments with nitryl chloride.

With nitryl fluoride.

Aliphatic compound	Product
Ethyl alcohol	Ethyl nitrate, acetaldehyde, acetic acid
n-Pentane	No reaction
Chloroform	No reaction
Carbon tetrachloride	No reaction
Carbon disulphide	Very little reaction

Aromatic compound	Solvent	Product
Benzene	—	Nitrobenzene (65%), *m*-dinitrobenzene (<5%)
Toluene	—	2 : 4-Dinitrotoluene (55%)
Bromobenzene	—	*p*- (60%) and *o*-Nitrobromobenzene (trace)
Nitrobenzene	—	*m*-Dinitrobenzene (trace)
Benzaldehyde	—	Benzoic acid (trace)
Phenol	CS_2	*p*- (trace) and *o*-Nitrophenol (trace)
Naphthalene	C_5H_{12}	1-Nitronaphthalene (35%)
Anthracene	$CHCl_3$	9-Nitroanthracene
Salicyclic acid	$PhNO_2$	5-Nitrosalicylic acid
Benzoic acid	CS_2	No reaction

(*m*-Cresol, anisole, diphenyl ether, aniline, furan, and quinoline gave tars.)

With nitryl chloride.

	Product (without solvent)	Solvent	Catalyst	Product (with solvent and catalyst)
Benzene	Nitrobenzene (27—35%)	HF	HF	Nitrobenzene (70%)
Benzene	—	CS_2	$AlCl_3$	Nitrobenzene (89%)
Toluene	—	,,	,,	*o*- (47%) and *p*-Nitrotoluene (24%)
Bromobenzene	—	,,	,,	*o*- (8%) and *p*-Nitrobromobenzene (67%)
Nitrobenzene	—	HF	BF_3	No reaction
Benzaldehyde	—	CS_2	$AlCl_3$	No reaction
Phenol	—	,,	,,	*o*- (trace) and *p*-Nitrophenol (trace)
Naphthalene	—	,,	,,	1-Nitronaphthalene (31%)
Salicylic acid	—	$PhNO_2$	$AlCl_3$	5-Nitrosalicylic acid (10%)
Benzoic acid	—	CS_2	$AlCl_3$	No reaction

The behaviour of the organic compounds used falls into three patterns : (*a*) the inert, comprising aliphatic hydrocarbons and deactivated aromatic compounds such as nitro-

benzene; (*b*) the normally nitrated; (*c*) the destroyed, comprising highly reactive aromatic materials, such as aniline, which rapidly gave tar. As was expected, those undergoing nitration gave the same nitro-compounds as result from the use of mixed acids. We believe that the nitration is due to the nitronium ion, NO_2^+, formed by dissociation of the nitryl fluoride in the liquid undergoing treatment. As may be seen from the Table, the products are qualitatively similar in character to those produced when nitryl chloride is employed. Unfortunately, only one quantitative comparison can be made, namely, in the reactions with benzene, where clearly the yield from nitryl chloride when used without a catalyst is about half that obtained with the fluoride. Other materials, *e.g.*, toluene, bromobenzene, and naphthalene, show more nitration with nitryl fluoride than with the chloride even when the latter is used with a catalyst. This suggests that nitryl fluoride stands higher than nitryl chloride in the series of nitrating agents of the type $X{\cdot}NO_2$, in which the nitrating power increases with the electron-accepting quality of X (see Gillespie and Millen, *Quart. Reviews*, 1948, **2**, 278).

Pyridine does not fall into any of the behaviour patterns mentioned above since, besides the volatile 3-nitropyridine which distils forward, there is left in the reaction vessel a viscous brown liquid. This undoubtedly contains fluorine and sets to a gum, on the surface of which appear white crystals. According to the analytical evidence these crystals and the polymer are very similar material, and are probably a hydrofluoride of 3-nitropyridine. Both substances react immediately with water to form an orange-brown precipitate which dissolves in acetone to give a clear orange solution. The solid is 2 : 6-dihydroxy-3-nitropyridine. This shows that water not only hydroxylates the two substances but also removes fluorine from them.

Experimental

Preparation of Nitryl Fluoride.—This was prepared, as previously described (*J.*, 1954, 1119), by passing a stream of fluorine (about 4 g./hr.) diluted with nitrogen (1 : 1 by vol.) over well-dried sodium nitrite. The nitryl fluoride was fractionated in a vacuum to free it from fluorine and nitrogen peroxide and stored in a bulb fitted with a "break-seal," whence it could be obtained after attaching the bulb to the rest of the apparatus.

Treatment of the Organic Compounds.—This was done in a Pyrex all-glass train, carrying a number of traps, which before use was carefully dried. When the organic material was a liquid, it was treated, in lots of about 5 c.c., by bubbling nitryl fluoride vapour through it; when a solid or a too reactive liquid, the compound was dissolved in an inert solvent such as *n*-pentane, carbon disulphide, chloroform, or nitrobenzene. Usually the reaction was very exothermic and to moderate its vigour the trap was cooled in ice. The treatment took only a few minutes to complete, after which the apparatus was flushed out with nitrogen to remove the excess of nitryl fluoride together with any hydrogen fluoride retained by the organic product; this was subsequently purified by such conventional means as fractionation, steam-distillation, and crystallisation.

Individual Reactions.—Ethyl alcohol : reaction was very vigorous, the alcohol boiling with the heat of reaction. Some alcohol–ethyl nitrate azeotropic mixture (b. p. 71·85°) distilled forward and was collected in the next trap. Other products were acetaldehyde and acetic acid from the oxidation of the alcohol.

n-*Pentane, chloroform, and carbon tetrachloride :* the liquids became yellow but, on distillation, the original liquid was recovered unchanged. The colour was caused by the release of nitrogen dioxide.

Carbon disulphide : in contradistinction to the behaviour with nitryl chloride, there appeared to be some action, too little, however, to justify investigation.

Benzene : a very exothermic reaction began at room temperature; the benzene boiled even when surrounded by ice, and became deep yellow. Fractionation yielded nitrobenzene (b. p. 210°; 65%) and *m*-dinitrobenzene (m. p. 89°; <5%).

Toluene : a very exothermic reaction began at room temperature and deposited a yellow solid from a yellow solution. Recrystallised from ether the solid proved to be 2 : 4-dinitrotoluene (Found : C, 46·1; H, 3·4; N, 15·7. Calc. for $C_7H_6O_4N_2$: C, 46·2; H, 3·3; N, 15·7%), m. p. 69° (yield 55%).

Naphthalene : treatment in *n*-pentane gave a yellow solid. Unchanged naphthalene was

leached out with *n*-pentane, and the nitro-compound, recrystallised from chloroform, was 1-nitronaphthalene (m. p. 61°; dark red solution with concentrated sulphuric acid; yield 30—40%).

Anthracene: treatment in chloroform solution caused a mildly exothermic reaction. The solution became brown and a precipitate was formed which, recrystallised from alcohol, proved to be 9-nitroanthracene (15%) (Found: C, 74·6; H, 3·5; N, 5·9. Calc. for $C_{14}H_9O_2N$: C, 75·3; H, 4·0; N, 6·3%).

Bromobenzene: reaction was so vigorous that reactants had to be cooled; a yellow solid was deposited which crystallised from alcohol as very pale yellow crystals (67%), m. p. 126°, of *p*-bromonitrobenzene (Found: C, 35·6; H, 2·4; N, 7·0. Calc. for $C_6H_4O_2NBr$: C, 35·6; H, 2·0; N, 6·9%). In addition a trace of solid, m. p. 40°, probably *o*-bromonitrobenzene was recovered.

Phenol: despite its being dissolved in carbon disulphide there was a tendency for the material to form tar and even to catch fire. The yellow product was separated by steam-distillation into two fractions which gave qualitative evidence of *o*- and *p*-nitrophenol, severally.

m-*Cresol, anisole, diphenyl ether, and aniline:* with all these substances there was a great chance of inflammation and, even when moderated by dilution and cooling, the reaction produced tars.

Salicylic acid: treatment in nitrobenzene gave a reddish-brown liquid and a pale yellow solid, m. p. 230°, was deposited which qualitative tests showed to be 5-nitrosalicylic acid.

Benzoic acid: treated in carbon disulphide, this showed no evidence of reaction.

Nitrobenzene: there was no reaction in the cold, but evidently some on warming since, on cooling, a few white flakes appeared which were probably *m*-dinitrobenzene.

Benzaldehyde: there was no nitration, but a little oxidation to benzoic acid.

Pyridine: except with very good cooling, the reaction was violently exothermic. A yellow solid (material A) condensed in the second trap and a reddish-brown viscous liquid which did not smell of pyridine remained in the reaction vessel (material B). Material A was 3-nitropyridine (10%), m. p. 40° (lit., 41°) (Found: C, 47·6; H, 4·0; N, 21·8. Calc. for $C_5H_2O_2N_2$: C, 48·4; H, 3·2; N, 22·6%).

Material B was a polymer which frothed badly when warmed in a vacuum and could not be distilled. In a desiccator it set to an orange-brown solid, on the surface of which a small growth of white crystals appeared. Both the polymer and the crystals contained fluorine and the three analyses, (i) and (ii) of the polymer and (iii) of the crystals, show a relationship [Found: (i) C, 41·3; H, 4·35; N, 11·0; (ii) C, 41·5; H, 4·1; N, 13·2; (iii) C, 39·1; H, 3·85; N, 11·3%] but are not readily fitted to any recognisable compound though not far from a hydrofluoride of 3-nitropyridine (Calc. for $C_5H_3O_2NF$: C, 46·2; H, 3·9; N, 10·8%). When added to water, both the polymer and the crystals yield an orange-brown solid and a colourless solution. The solid, washed with water, light petroleum, and ether, and dried in a vacuum, was a pale orange-brown powder which melted with decomposition at 300°, and was soluble in acetone and in alkali to a yellow solution. The analysis left little doubt that it was 2:6-dihydroxy-3-nitropyridine (Found: C, 38·3; H, 2·5; N, 18·2. Calc. for $C_5H_4O_4N_2$: C, 38·5; H, 2·6; N, 18·0%).

The authors express their indebtedness to the General Chemicals Division of Imperial Chemical Industries Limited, Widnes, for the fluorine cell used, and to the Salters' Company for a Scholarship which enabled one of them (G. H.) to take part in the work.

KING'S COLLEGE, NEWCASTLE-ON-TYNE, 1. [*Received, May 27th,* 1954.]

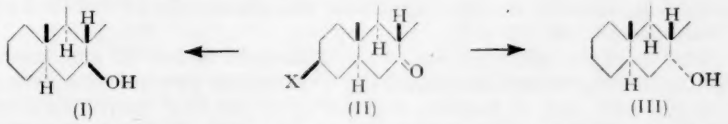
Steroids and Walden Inversion. Part XVI. The Epimeric Cholestan-7-ols.*

By R. J. W. Cremlyn and C. W. Shoppee.

[Reprint Order No. 5422.]

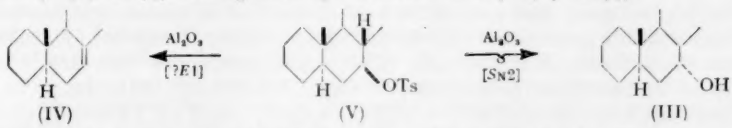
Cholestan-7α-ol has been prepared from cholestan-7-one by reduction with lithium aluminium hydride. The configurations of the epimeric cholestan-7-ols have been determined by conversion with sodium *n*-butoxide of the less thermodynamically stable 7α- into the 7β-epimeride, and by study of the relative rates of alkaline hydrolysis of 7α- and 7β-benzoyloxycholestane, whose elimination reactions have also been studied.

A single cholestan-7-ol, m. p. 119°, $[\alpha]_D$ +51°, has been obtained by reduction with sodium and amyl alcohol of 7-oxocholestan-3β-yl chloride (II; X = Cl) (Marker, Kamm, Fleming, Popkin, and Wittle, *J. Amer. Chem. Soc.*, 1937, **59**, 619) or of cholestan-7-one (II; X = H) (Heilbron, Shaw, and Spring, *Rec. Trav. chim.*, 1938, **57**, 529; Eck and Hollingsworth, *J. Amer. Chem. Soc.*, 1941, **63**, 2986). Heilbron *et al.* correctly considered their compound to be the 7β-epimeride (I; equatorial) cf. Barton, *Experientia*, 1950, **6**, 316, footnote to Table 1. It has subsequently been prepared, m. p. 112°, $[\alpha]_D$ +38°, by desulphurisation with nickel under pressure of 3ξ-ethylthiocholest-5-en-7-one by Ralls, Dodson, and Riegel (*ibid.*, 1949, **71**, 3320), and we have prepared it, m. p. 113°, $[\alpha]_D$ +52°, by reduction of the ketone (II; X = H) with sodium and butan-1-ol.



Hydrogenation of the ketone (II; X = H) with platinum black in acetic acid appeared to give cholestane and cholestan-7β-ol (65%) †; a similar result was obtained by use of aluminium *iso*propoxide in *iso*propyl alcohol (yield 73%). Reduction with lithium aluminium hydride gave a small quantity of cholestane, cholestan-7β-ol (~55%), m. p. 113°, $[\alpha]_D$ +52°, and cholestan-7α-ol (~25%) (III), m. p. 98°, $[\alpha]_D$ +11°; the 7α-alcohol was characterised as acetate, benzoate, and 3 : 5-dinitrobenzoate, but the toluene-*p*-sulphonate could not be prepared.

The observation that only cholestan-7β-ol gave a toluene-*p*-sulphonate appeared to afford a method for separation of the epimerides (I, III), which form mixed crystals and require careful and tedious chromatography. It was found, however, that 7β-toluene-*p*-sulphonyloxycholestane (V) is partly decomposed by neutralised aluminium oxide in pentane to give cholest-7-ene (IV), m. p. 82°, $[\alpha]_D$ +12° (cf. Eck and Hollingsworth, *loc. cit.*; Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, 1949, p. 248), whilst use of alkaline aluminium oxide in pentane furnished cholest-7-ene (IV) (~30%) accompanied by cholestan-7α-ol (III) (~60%).



The transformation (V ⟶ III) with inversion of configuration at $C_{(7)}$ renders practicable the conversion of the more thermodynamically stable epimeride (I) into the less thermodynamically stable epimeride (III). The production of cholest-7-ene (IV) by an apparent *cis*-elimination may occur by unimolecular heterolysis [*E*1] with subsequent

* Part XV, *J.*, 1954, 3418.

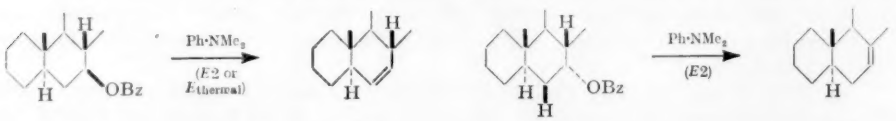
† After this work was completed, Dauben, Dickel, Jeger, and Prelog (*Helv. Chim. Acta*, 1953, **36**, 325) by hydrogenation of (II) with platinum oxide in acetic acid obtained cholestane, cholestan-7β-ol (I), m. p. 114—115°, $[\alpha]_D$ +55°, and cholestan-7α-ol (III), m. p. 98°, $[\alpha]_D$ +10°.

internal depolarisation of the resulting carbonium ion; similar observations of apparent *cis*-elimination have recently been made concerning the conversion of 11-hydroxy-steroids into 9(11)-unsaturated steroids (Fried and Sabo, *J. Amer. Chem. Soc.*, 1953, **75**, 2273; Casanova, Shoppee, and Summers, *J.*, 1953, 2983; Bernstein, Littel, and Williams, *J. Amer. Chem. Soc.*, 1953, **75**, 4830; Bernstein, Lenhard, and Williams, *J. Org. Chem.*, 1954, **19**, 41; Herzog, Payne, and Hershberg, *J. Amer. Chem. Soc.*, 1954, **76**, 930).

The conversion of cholestan-7α-ol (III; OH, axial) into the more thermodynamically stable cholestan-7β-ol (I; OH, equatorial) occurs by treatment with sodium in boiling butan-1-ol, and is consistent with the configurations assigned. Confirmation of these assignments has been obtained by study of the relative rates of alkaline hydrolysis [S_N2] (cf. Barton, *Experientia*, 1950, **6**, 312) of the epimeric 7-benzoyloxy-cholestanes; the 7β-benzoate (VI; OBz, equatorial) was found to be hydrolysed roughly thrice as fast as the 7α-benzoate (VIII; OBz, axial). It is interesting to observe that the 1 : 3-compressions of the 7α-benzoyloxy-group by the axial hydrogen atoms attached to $C_{(5)}$, $C_{(9)}$, and $C_{(14)}$ are more effective than the 1 : 4-compressions of the 7β-benzoyloxy-group by the angular methyl groups attached to $C_{(10)}$ and $C_{(13)}$; this may be compared with the corresponding deduction (Shoppee, *Hormones and Vitamins*, 1951, **8**, 288) from the relative rates of alkaline hydrolysis of the epimeric cholestan-3-yl acetates and benzoates which are 3β>3α [acetates, 3·1 : 1; benzoates, 3·4 : 1] (Ruzicka, Furter, and Goldberg, *Helv. Chim. Acta*, 1938, **21**, 498).

Further support for our assignment of configuration is provided by molecular-rotation differences. For 7β-acetoxycholestane ΔA is found to be +172°, whilst the standard value for ΔA[5α] : 7β is +208° (Barton and Klyne, *Chem. and Ind.*, 1948, 755); for 7α-acetoxy-cholestane ΔA is −144° in excellent agreement with the standard value for ΔA[5α] : 7α of −143° (Barton and Klyne, *loc. cit.*).

The pyrolysis of the epimeric 7-benzoyloxycholestanes at 320°/17 mm. has been examined. It has been shown that mechanistically unimolecular pyrolytic elimination reactions require *cis*-geometry and, if possible, coplanarity of the four centres involved (Barton, *J.*, 1949, 2714). 7β-Benzoyloxycholestane (VI), in which the 6β- or 8β-hydrogen atom (axial) and the 7β-benzoyloxy-group (equatorial) are *cis* but cannot be coplanar, was completely resistant to pyrolysis and was recovered unchanged. 7α-Benzoyloxycholestane (VIII), in which only the 6α-hydrogen atom (equatorial) is *cis* to the 7α-benzoyloxy-group



(VI) (VII) (VIII) (IV)

(axial) but not coplanar, was also partly unchanged by pyrolysis at 320°/17 mm., but gave pure cholest-6-ene (VII), m. p. 85°, $[\alpha]_D$ −88°, in good agreement with the constants, m. p. 86—87°, $[\alpha]_D$ −88°, previously reported (Fischer, Lardelli, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 1577).

A study was also made of the action of dimethylaniline at 194° on the epimeric 7-benzoyloxycholestanes; this method for 1 : 2-elimination of benzoic acid has been used in connection with the preparation of 7-dehydrocholesterol by Haslewood (*J.*, 1938, 224) and by Buser (*Helv. Chim. Acta*, 1947, **30**, 1384). Both epimerides were largely unchanged, but whereas 7β-benzoyloxycholestane (VI) gave cholest-6-ene (VII), m. p. 79—82°, $[\alpha]_D$ −70° [probably contaminated with ~10% of cholest-7-ene (IV)], 7α-benzoyloxycholestane (VIII) gave cholest-7-ene (IV), m. p. 82°, $[\alpha]_D$ +12°. The elimination (VI ⟶ VII) could involve either the equatorial 6α-hydrogen atom *trans* to the equatorial 7β-benzoyloxy-group (*E*2) or the axial 6β-hydrogen atom *cis* to the equatorial 7β-benzoyloxy-group ($E_{thermal}$); the elimination (VIII ⟶ IV), involving the tertiary axial 8β-hydrogen atom, however, suggests that the dimethylaniline functions as a base and not as a thermal medium, and that the reaction is an ionic elimination (*E*2) of super-Saytzeff type (cf. Dhar, Hughes, Ingold, Mandour, Maw, and Woolf, *J.*, 1948, 2093) requiring *trans*-geometry and coplanarity of the four participating centres (cf. Curtin, *J. Amer. Chem. Soc.*, 1953, **75**, 6011).

Experimental

For general directions see *J.*, 1954, 3418. $[\alpha]_D$ were measured in $CHCl_3$, and ultra-violet absorption spectra were determined in ethanol on a Unicam SP.500 spectrophotometer with corrected scale.

Cholestan-7-one.—Cholesteryl acetate was oxidised with chromium trioxide–acetic acid (Fieser, Fieser, and Chakravarti, *J. Amer. Chem. Soc.*, 1949, **71**, 2226) to 7-oxocholesteryl acetate, which was converted in 70% yield into cholesta-3 : 5-dien-7-one, m. p. 112—114°, by alkaline hydrolysis, dehydration with anhydrous copper sulphate in benzene at 80°, and chromatography on aluminium oxide [eluant : benzene–pentane (1 : 2)] (cf. Mauthner and Suida, *Monatsh.*, 1896, **17**, 579; Stavely and Bergmann, *J. Org. Chem.*, 1937, **1**, 567). Hydrogenation of cholesta-3 : 5-dien-7-one as described by Heilbron, Shaw, and Spring (*Rec. Trav. chim.*, 1938, **57**, 529) gave cholestan-7-one, plates (from acetone), m. p. 116—118°, characterised as the 2 : 4-*dinitrophenylhydrazone*, yellow plates (from benzene–ethanol), m. p. 205—207° [Found (after drying at 100°/0·01 mm. for 2 hr.) : C, 69·6; H, 8·7. $C_{33}H_{50}O_4N_4$ requires C, 69·9; H, 8·9%].

Cholestan-7β-ol.—This alcohol, m. p. 112—113°, $[\alpha]_D$ +52° (*c*, 1·1), prepared by reduction of cholestan-7-one with sodium in boiling butan-1-ol, gave no precipitate with a 0·5% solution of digitonin in ethanol, and was characterised by the *acetate* (acetic anhydride–pyridine at 20°), m. p. 66°, $[\alpha]_D$ −61° (*c*, 0·69), after chromatography and recrystallisation from ether–methanol [Found (after drying at 50°/0·02 mm. for 9 hr.) : C, 80·9; H, 11·4. $C_{29}H_{50}O_2$ requires C, 80·9; H, 11·7%], the *benzoate* (benzoyl chloride–pyridine at 20°), m. p. 106—108°, $[\alpha]_D$ +87° (*c*, 1·4), after recrystallisation from acetone [Found (after drying at 50°/0·02 mm. for 9 hr.) : C, 83·2; H, 10·7. $C_{34}H_{52}O_2$ requires C, 82·9; H, 10·6%], the 3 : 5-*dinitrobenzoate*, m. p. 151—152°, $[\alpha]_D$ +105° (*c*, 2·65), after two recrystallisations from acetone [Found (after drying at 20°/0·01 mm. for 12 hr.) : C, 70·0; H, 8·8. $C_{34}H_{50}O_6N_2$ requires C, 70·0; H, 8·7%], and the *toluene-p-sulphonate* (toluene-*p*-sulphonyl chloride–pyridine at 20° for 60 hr.), m. p. 158—159°, $[\alpha]_D$ +38° (*c*, 1·14), after recrystallisation from acetone [Found (after drying at 60°/0·01 mm. for 10 hr.) : C, 75·3; H, 10·2. $C_{34}H_{54}O_3S$ requires C, 75·2; H, 10·0%].

Cholestan-7α-ol.—Cholestan-7-one (5·6 g.) was reduced with lithium aluminium hydride (4·8 g.) in ether according to the directions of Shoppee and Summers (*J.*, 1950, 687). The resultant colourless oil was chromatographed on aluminium oxide (450 g.) in pentane (58 fractions); elution with pentane gave cholestane (108 mg.), m. p. 78—80° after recrystallisation from acetone. Elution with benzene–pentane (1 : 6) gave *cholestan-7α-ol* (1·27 g.), m. p. 94—97°, raised by recrystallisation from methanol to 98°, $[\alpha]_D$ +11° (*c*, 1·04) [Found (after drying at 60°/0·01 mm. for 10 hr.) : C, 83·5; H, 12·4. $C_{27}H_{48}O$ requires C, 83·4; H, 12·4%]. Further elution with benzene–pentane (1 : 6) gave mixtures of the epimerides, m. p. 90—106°, whilst use of benzene–pentane (1 : 3) gave cholestan-7β-ol (2·4 g.), m. p. 108—112°, raised by recrystallisation from ether–methanol to 112—113°.

Cholestan-7α-ol was characterised by preparation of the *acetate*, m. p. 117°, $[\alpha]_D$ −12° (*c*, 1·2), after two recrystallisations from acetone–methanol (1 : 1) [Found (after drying at 60°/0·01 mm. for 6 hr.) : C, 81·0; H, 11·6%], the *benzoate*, m. p. 163—165°, $[\alpha]_D$ −22° (*c*, 0·56), after two recrystallisations from acetone [Found (after drying at 65°/0·01 mm. for 6 hr.) : C, 82·9; H, 10·4%], and the 3 : 5-*dinitrobenzoate*, m. p. 176—177°, $[\alpha]_D$ −24° (*c*, 2·1), after two recrystallisations from acetone [Found (after drying at 20°/0·01 mm. for 12 hr.) : C, 70·0; H, 8·7%].

Conversion of Cholestan-7α- into Cholestan-7β-ol.—Cholestan-7α-ol (m. p. 98°; 100 mg.) was dissolved in butan-1-ol (purified according to the instructions of Clarke, Robinson, and Smith *J.*, 1927, 2647), and sodium was gradually added to the refluxing solution until no more would dissolve. After 6 hr., butanol was largely removed under reduced pressure, and the mixture worked up in the usual way to yield an oil (80 mg.). This crystallised and by recrystallisation from ether–methanol gave cholestan-7β-ol, m. p. and mixed m. p. 110—112°.

Conversion of Cholestan-7β- into Cholestan-7α-ol.—When 7β-toluene-*p*-sulphonyloxycholestane (75 mg.), dissolved in pentane, was introduced on to a column of neutralised aluminium oxide (4 g.; Reichstein and Shoppee, *Discuss. Faraday Soc.*, 1949, **7**, 305), prepared in pentane; elution with pentane (100 c.c.) gave after evaporation a colourless oil, which crystallised when rubbed with acetone–methanol; recrystallisation from acetone afforded cholest-7-ene, m. p. and mixed m. p. 78°, $[\alpha]_D$ +12° (*c*, 1·07), giving a yellow colour with tetranitromethane–chloroform. Similar treatment of the ester (100 mg.) in pentane with alkaline aluminium oxide (6 g.; Spence type H, 200 mesh, activity ~11, scale of Brockmann and Schodder, *Ber.*, 1941, **74**, 73), and

elution with pentane (100 c.c.), gave a solid (28 mg.), which by recrystallisation from methanol furnished cholest-7-ene, m. p. and mixed m. p. 80—82°. Further elution with benzene–pentane (1 : 1) yielded a solid (65 mg.), which by recrystallisation from acetone gave cholestan-7α-ol, m. p. and mixed m. p. 97—99°.

In an attempt to utilise the non-formation of a toluene-*p*-sulphonate by cholestan-7α-ol to separate the epimeric cholestan-7-ols, the isomorphous mixture of cholestan-7-ols (m. p. 86—92°; 1 g.) was treated with toluene-*p*-sulphonyl chloride (800 mg.) in pyridine (10 c.c.), and the oily product (1·1 g.) was dissolved in pentane and chromatographed on neutralised aluminium oxide (38 g.). Elution with pentane gave cholest-7-ene (393 mg.), m. p. 74—80° after crystallisation from acetone, giving a yellow colour with tetranitromethane–chloroform. Elution with benzene–pentane (1 : 1) gave crystals (130 mg.), which on recrystallisation from acetone gave cholestan-7α-ol, m. p. and mixed m. p. 95—98°; further elution with benzene–pentane (1 : 1) gave a colourless oil (84 mg.), which solidified and by recrystallisation from ether–methanol gave cholestan-7β-ol, m. p. and mixed m. p. 110—112°.

Alkaline Hydrolysis of the 7-Benzoyloxycholestanes.—Samples of the epimeric benzoates (40 mg.) were dissolved in methanol (5 c.c.), mixed each with 2·00 c.c. of methanolic 0·243N-sodium hydroxide, and heated under reflux with exclusion of moisture and carbon dioxide; corresponding blank experiments were run, and after various periods the amount of alkali used was estimated by titration with 0·048N-hydrochloric acid (cf. Reichstein and Shoppee, *Helv. Chim. Acta*, 1940, **23**, 979). The following results were obtained:

	7β-Benzoyloxycholestane (VI)								7α-Benzoyloxycholestane (VIII)					
Time of reflux (hr.)	3	8	12	25	46	72	168	260	30	47	72	150	288	430
0·233N-NaOH used (c.c.)	0·14	0·16	0·18	0·42	0·52	0·70	1·24	1·45	0·15	0·20	0·38	0·50	0·84	1·20
Hydrolysis (%)	9·2	10·5	11·8	27·6	34·2	46	82·7	95·4	9·8	13·2	25	33	55·3	80

Pyrolysis of the 7-Benzoyloxycholestanes.—(*a*) 7β-Benzoyloxycholestane (m. p. 106—108°; 1·4 g.) was heated in a stream of dry oxygen-free nitrogen at 320°/17 mm. for 3 hr.; the material was then distilled rapidly at 0·02 mm. The usual working up yielded no benzoic acid; the neutral product was chromatographed on neutralised aluminium oxide in pentane. Elution with pentane (2 × 150 c.c.) furnished crystals (1·2 g.), which by recrystallisation from acetone gave 7β-benzoyloxycholestane, m. p. and mixed m. p. 106—108°. The material (189 mg.) from the acetone mother-liquor was pyrolysed again, at 290—350°/17 mm. for 3 hr., but after similar treatment yielded only unchanged 7β-benzoyloxycholestane (170 mg.), m. p. 105—108°.

(*b*) 7α-Benzoyloxycholestane (m. p. 164—165°; 836 mg.) was pyrolysed similarly, and gave some benzoic acid. The neutral product crystallised spontaneously and was chromatographed on neutralised aluminium oxide (25 g.); elution with pentane (3 × 100 c.c.) gave a solid (560 mg.), which by recrystallisation from acetone furnished 7α-benzoyloxycholestane, m. p. and mixed m. p. 165—166°. The material (140 mg.) from the acetone mother-liquor by repeated recrystallisation from acetone gave more unchanged starting material, and finally a fraction, m. p. 82—86°, giving a yellow colour with tetranitromethane. Recrystallisation from acetone gave cholest-6-ene (20 mg.), m. p. 83—85°, $[\alpha]_D$ −88° (*c*, 0·70), $\lambda_{max.}$ 207 mμ, log ε 3·28.

Treatment of the 7-Benzoyloxycholestanes with Dimethylaniline.—(*a*) 7β-Benzoyloxycholestane (200 mg.) was refluxed with dimethylaniline for 20 hr. After removal under reduced pressure of most of the dimethylaniline, the residual oil was worked up in the usual way to give a colourless oil (180 mg.), which crystallised spontaneously and by recrystallisation from acetone gave 7β-benzoyloxycholestane, m. p. and mixed m. p. 106—108°. Repeated recrystallisation of material from the mother-liquor gave further small amounts of the 7β-benzoate, and finally a product, m. p. 76°, giving a yellow colour with tetranitromethane–chloroform. Recrystallisation of this from acetone gave nearly pure cholest-6-ene (10 mg.), m. p. 79—82°, $[\alpha]_D$ −70° (*c*, 0·47).

(*b*) 7α-Benzoyloxycholestane (200 mg.) was refluxed with dimethylaniline for 12 hr. The product (175 mg.) crystallised, and by recrystallisation from acetone gave 7α-benzoyloxycholestane, m. p. and mixed m. p. 165—167°. The mother-liquor gave a second crop, m. p. 164—166°, and, after removal of further small amounts of the 7α-benzoate, afforded by crystallisation from acetone cholest-7-ene (9 mg.), m. p. and mixed m. p. 81—83°, $[\alpha]_D$ +12° (*c*, 0·88), $\lambda_{max.}$ 212 mμ, log ε 3·45, giving a yellow colour with tetranitromethane–chloroform.

One of us (R. J. W. C.) acknowledges the support of the Department of Scientific and Industrial Research. We thank Glaxo Laboratories Ltd. for gifts of cholesterol.

UNIVERSITY OF WALES, UNIVERSITY COLLEGE OF SWANSEA. [*Received, May 28th*, 1954.]

Cereal Gums. Part I. The Methylation of Barley Glucosans.

By G. O. Aspinall and R. G. J. Telfer.

[Reprint Order No. 5440.]

Two samples of water-soluble lævorotatory glucosan from barley grain have been shown to be composed solely of D-glucose residues. Hydrolysis of the methylated polysaccharides gave 2 : 3 : 6- and 2 : 4 : 6-tri-*O*-methyl-D-glucoses. It is concluded that these barley glucosans contain unbranched chains of β-D-glucopyranose residues with approximately equal proportions of 1 : 3- and 1 : 4-linkages.

The cereal gums are the non-starchy water-soluble polysaccharides found in cereal grains (for a review see Preece, *Proc. Eur. Brew. Conv., Brighton*, 1951, 213). Hydrolysis of various cereal gums has shown that residues of D-glucose, D-xylose, and L-arabinose are always present and sometimes in addition smaller amounts of D-galactose and D-mannose. Structural investigations so far carried out have been concerned mainly with fractions rich in pentosan isolated from wheat. Ford and Peat (*J.*, 1941, 856) isolated from wheat grain a water-soluble polysaccharide associated with β-amylase and showed that a highly branched molecule containing L-arabofuranose, D-xylopyranose and D-galactopyranose residues was present. More recently, Perlin (*Cereal Chem.*, 1951, **28**, 370, 382) has shown wheat flours to contain a mixture of water-soluble pentosans and hexosans, the pentosan being an araboxylan containing L-arabofuranose residues attached as side-chains to a main chain of 1 : 4-linked β-D-xylopyranose residues.

A considerable advance in understanding the nature and properties of these water-soluble gums has been made recently by Preece and Mackenzie (*J. Inst. Brewing*, 1952, **58**, 353) who have succeeded in preparing a lævorotatory glucosan free from pentosan by fractionation of barley extracts. Barley grain, previously extracted with boiling 80% aqueous ethanol to remove free sugars and oligosaccharides and to inactivate enzymes, was extracted with water at 40° and the aqueous extracts were fractionated by the addition of ammonium sulphate. A sample of barley glucosan prepared under these mild conditions was kindly placed at our disposal for structural investigations by Professor I. A. Preece and Dr. K. G. Mackenzie of the Heriot-Watt College, Edinburgh. We were also provided with a sample of glucosan isolated from barley extracts modified during the preparation by digestion with an enzymically active barley extract. These glucosans are of great importance in malting as Preece and Mackenzie (*loc. cit.*) have shown that barley enzymes, during germination, produce a rapid hydrolysis so that little of these polysaccharides survives in malt.

Both samples of glucosan (from unmodified and from modified barley) were lævorotatory ($[\alpha]_D^{15}$ −12·5° and −13° respectively in H_2O) and gave on hydrolysis only glucose (96—97%). Hydrolysis of the corresponding methylated glucosans gave mixtures of 2 : 3 : 6- and 2 : 4 : 6-tri-*O*-methyl-D-glucose together with small quantities of an unidentified di-*O*-methyl-glucose (probably arising from undermethylation of the polysaccharides and/or demethylation during hydrolysis). Both tri-*O*-methyl-D-glucoses were obtained crystalline and the 2 : 4 : 6-isomer was also converted into its aniline derivative. No evidence was obtained for the presence of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose in the hydrolysate of the methylated unmodified glucosan, but chromatographic evidence suggested that a small quantity (<0·5%) of this sugar was present in the hydrolysate of the methylated modified glucosan. The proportions of the 2 : 3 : 6- and 2 : 4 : 6-tri-*O*-methyl-D-glucoses were estimated by following the changes in optical rotation in cold methanolic hydrogen chloride of the hydrolysates from both methylated glucosans (cf. Granichstädten and Percival, *J.*, 1943, 54) : the contributions of minor components being neglected, the two isomers were found to be present in practically equal amounts.

Molecular-weight determinations by the isothermal-distillation method and by osmotic-pressure measurements (by the courtesy of Mr. W. N. Broatch and Dr. C. T. Greenwood) gave values of *ca.* 20,000 (degree of polymerisation *ca.* 100) for the methylated glucosan

from unmodified barley. It is difficult, therefore, to understand the complete absence of tetra-*O*-methyl-D-glucose arising from a non-reducing end-group unless a loop structure is postulated for the polysaccharide. However, in the light of our knowledge of the structure of other polysaccharides, such a loop appears unlikely, although it cannot be excluded. Although some evidence was obtained for the presence of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose in the hydrolysate of the methylated glucosan from modified barley, the quantity indicated was considerably smaller than would be expected from a linear molecule of similar size. In all other respects, the two samples of glucosan were closely similar. An ultracentrifugal examination of the glucosan from unmodified barley (by the courtesy of Dr. C. T. Greenwood) indicated the presence of only one component and thus suggested the presence of a single polysaccharide containing 1 : 3- and 1 : 4-linked β-D-glucopyranose residues rather than a mixture of two molecular species.

During the present investigation the preliminary results of structural investigations of the water-soluble polysaccharides of barley grain have been published elsewhere. Gilles, Meredith, and Smith (*Cereal Chem.*, 1952, **29**, 314) showed that the aqueous extract of barley flour (barley gum) gave glucose, xylose, and arabinose on hydrolysis, but did not attempt the isolation of individual components. Fractionation of methylated barley gum gave three components : (*a*) a methylated araboxylan (cf. Perlin, *loc. cit.*); (*b*) a methylated poly-α-glucosan, similar to methylated starch; and (*c*) a methylated poly-β-glucosan ($[\alpha]_D$ −9° in acetone). These workers, however, isolated only 2 : 3 : 6-tri-*O*-methyl-D-glucose from the hydrolysis of the methylated poly-β-glucosan and concluded that this component was probably structurally related to cellulose. It appears more likely that this component was similar to our methylated polysaccharides.

The present investigation indicates that barley glucosans contain unbranched chains of β-D-glucopyranose residues containing approximately equal numbers of 1 : 3- and 1 : 4-linkages. These polysaccharides are therefore structurally similar to lichenin (Meyer and Gürtler, *Helv. Chim. Acta*, 1947, **30**, 751; Chanda and Hirst, unpublished work). It is interesting that the enzyme lichenase is found in the seeds of most plants (Karrer and his co-workers, *Helv. Chim. Acta*, 1924, **7**, 144, 159, 916) and that the isolation of lichenin from oat seeds has been claimed (Morris, *J. Biol. Chem.*, 1942, **142**, 881). Preece and Mackenzie's study (*J. Inst. Brewing*, 1952, **58**, 457) of the distribution of pentosans and hexosans in the water-soluble gums of the common cereals (including oats) suggests that the so-called lichenin from oats is similar to the glucosans of barley. Further investigations will be necessary before it can be decided whether these glucosans are truly linear in structure and whether the 1 : 3- and 1 : 4-linkages are regularly or randomly distributed.

Experimental

Paper partition chromatography was carried out on Whatman No. 1 filter paper with the following solvent systems : (*a*) ethyl acetate–acetic acid–water (3 : 1 : 3; v/v; top layer); (*b*) butan-1-ol–ethanol–water (4 : 1 : 5; v/v; top layer); (*c*) benzene–ethanol–water (169 : 47 : 15; v/v; top layer clarified with ethanol).

Glucosan from unmodified barley

The polysaccharide was prepared, and kindly made available to us, by Professor I. A. Preece and Dr. K. G. Mackenzie (see *J. Inst. Brew.*, 1952, **58**, 353). It had $[\alpha]_D^{15}$ −12·5° (*c*, 1·0 in H_2O) and chromatographic examination of the hydrolysate (Hirst and Jones, *J.*, 1949, 1569) in solvent (*a*) showed the presence of glucose (97%) only.

Methylation of the Glucosan.—The glucosan (6·5 g.) was methylated five times with methyl sulphate and sodium hydroxide solution under nitrogen at room temperature and once with methyl iodide and silver oxide, and the product (6·8 g.) (Found : OMe, 45·0%) isolated by dissolution in chloroform. Fractionation was effected by refluxing chloroform–light petroleum (b. p. 60—80°) mixtures of different compositions. Two main fractions were obtained and these were combined for subsequent work :

Fraction	% of $CHCl_3$ in solvent	$[\alpha]_D^{17}$ (*c*, 1·0 in $CHCl_3$)	OMe, %	Wt. (g.)
1	20	−5·0°	44·8	2·5
2	25	−5·5	45·0	2·1

Hydrolysis of Methylated Glucosan.—The methylated glucosan (4·1 g.) was refluxed with methanolic 1% hydrogen chloride (200 c.c.) for 6 hr. (constant rotation). Then the solution was neutralised with silver carbonate and concentrated, and the resultant syrup was hydrolysed on the water-bath with 2% hydrochloric acid (160 c.c.) for 3 hr. (constant rotation). After neutralisation with silver carbonate the aqueous solution was concentrated to a syrup (4·27 g.). Chromatographic examination in solvent (*b*) showed the presence of 2 : 3 : 6- and 2 : 4 : 6-tri-*O*-methylglucoses and a trace of a di-*O*-methylglucose.

Separation of Methylated Sugars and Examination of Fractions.—The syrup (3·79 g.) was fractionated on cellulose (70 × 3 cm.) (Hough, Jones, and Wadman, *J.*, 1949, 2511) with light petroleum (b. p. 100—120°)–butanol (7 : 3), saturated with water, as eluant, to give five fractions.

Fraction 1. The syrup (0·808 g.) was non-reducing. A sample was further hydrolysed and chromatographic examination of the hydrolysate showed the presence of 2 : 3 : 6- and 2 : 4 : 6-tri-*O*-methylglucoses.

Fraction 2. Chromatographic examination of the syrup (0·188 g.) showed the presence of 2 : 3 : 6-tri-*O*-methylglucose together with a small quantity of a substance travelling faster on the chromatogram. Separation on filter sheets with solvent (*c*) gave fractions 2*a* (0·152 g.) and 2*b* (0·030 g.). Fraction 2*a* crystallised and after two recrystallisations from dry ether had m. p. 120—122° (unchanged on admixture with authentic 2 : 3 : 6-tri-*O*-methyl-D-glucose, but depressed on admixture with authentic 2 : 4 : 6-tri-*O*-methyl-D-glucose) and $[\alpha]_D^{16}$ +70° (equil.) (*c*, 1·0 in H_2O) (Found : C, 48·5; H, 7·9; OMe, 41·2. Calc. for $C_9H_{18}O_6$: C, 41·9; H, 8·1; OMe, 41·9%).

Fraction 3. Chromatographic examination of the syrup (2·847 g.) showed 2 : 3 : 6- and 2 : 4 : 6-tri-*O*-methylglucose. Fractions 1, 2*b*, and 3 were combined and rehydrolysed to give a syrup (3·51 g.), which had $[\alpha]_D^{16}$ +70° ⟶ +18° (*c*, 1·9 in methanolic 1% hydrogen chloride) and showed only 2 : 3 : 6- and 2 : 4 : 6-tri-*O*-methylglucose on the chromatogram.

Fraction 4. The syrup (0·238 g.) crystallised and after two recrystallisations from dry ether had m. p. and mixed m. p. (with authentic 2 : 4 : 6-tri-*O*-methyl-D-glucose) 120—122° and $[\alpha]_D^{17}$ +72° (equil.) (*c*, 1·5 in H_2O) (Found : C, 48·6; H, 7·8; OMe, 41·4. Calc. for $C_9H_{18}O_6$: C, 48·6; H, 8·1; OMe, 41·9%). The derived 2 : 4 : 6-tri-*O*-methyl-*N*-phenyl-D-glucosylamine had m. p. 144—145° (from ethanol–light petroleum) and 162—164° (from ethyl acetate).

Fraction 5. The syrup (14 mg.), which showed a mixture of tri-, di-, and mono-*O*-methylglucose on the chromatogram, was not examined further.

Estimation of the Relative Proportions of Tri-O-methylglucoses.—A sample (*ca.* 300 mg.) of the hydrolysate of the methylated glucosan was rehydrolysed with 2% hydrochloric acid (30 c.c.) for 7 hr. on the water-bath. After neutralisation of the hydrolysate with silver carbonate, concentration of the solution gave a syrup which showed $[\alpha]_D^{18}$ +61° ⟶ +12° (*c*, 1·32 in methanolic 1% hydrogen chloride). A synthetic mixture of 2 : 3 : 6- (46%) and 2 : 4 : 6-tri-*O*-methyl-D-glucose (54%) showed $[\alpha]_D$ +71° ⟶ +18° (*c*, 1·0 in methanolic 1% hydrogen chloride).

Glucosan from modified barley

The glucosan had $[\alpha]_D^{15}$ −13° (*c*, 0·88 in H_2O) and chromatographic examination of the hydrolysate (Hirst and Jones, *loc. cit.*) in solvent (*a*) showed the presence of glucose (96%) only.

Methylation of the Glucosan.—The glucosan (4·5 g.) was methylated six times with methyl sulphate and sodium hydroxide solution under nitrogen at room temperature, and twice with methyl iodide and silver oxide. The product (3·7 g.) (OMe, 45·0%), $[\alpha]_D^{16}$ −5·3° (*c*, 1·0 in $CHCl_3$), was purified by precipitation from chloroform solution with light petroleum (b. p. 40—60°).

Hydrolysis of Methylated Glucosan.—The methylated glucosan (3·0 g.) was refluxed with methanolic 1% hydrogen chloride (175 c.c.) for 7 hr. (constant rotation). After neutralisation with silver carbonate the residual syrup was hydrolysed on the water-bath with 2% hydrochloric acid (150 c.c.) for 10 hr., the hydrolysate was neutralised with silver carbobate and the solution was taken to dryness to give a syrup (2·96 g.). Paper chromatographic examination in solvents (*b*) and (*c*) showed the presence of 2 : 3 : 6- and 2 : 4 : 6-tri-*O*-methylglucose together with traces of tetra-*O*-methylglucose and a di-*O*-methylglucose.

Separation of Methylated Sugars and Examination of Fractions.—The syrup (2·68 g.) was fractionated on cellulose (70 × 3 cm.) with light petroleum (b. p. 100—120°)–butanol (7 : 3), saturated with water, as eluant, to give six fractions.

Fraction 1. Chromatographic examination of the syrup (12 mg.) showed the presence of 2 : 3 : 4 : 6-tetra-*O*-methylglucose. The syrup, however, did not crystallise when seeded with authentic tetra-*O*-methyl-D-glucose and chromatographic examination after further hydrolysis

showed that it also contained an approximately equal amount of methyl 2 : 3 : 6-tri-*O*-methyl-D-glucoside.

Fraction 2. The syrup (0·41 g.) was non-reducing and was rehydrolysed with 2% hydrochloric acid (20 c.c.). The syrupy hydrolysate (0·40 g.) was examined chromatographically and shown to contain a mixture of 2 : 3 : 6- and 2 : 4 : 6-tri-*O*-methylglucose.

Fraction 3. The syrup (1·15 g.) was chromatographically pure and crystallised. Two recrystallisations from dry ether gave 2 : 3 : 6-tri-*O*-methyl-D-glucose, m. p. and mixed m. p. 122—123°, $[\alpha]_D^{17}$ +71° (equil.) (*c*, 1·1 in H_2O) (Found: OMe, 41·5. Calc. for $C_9H_{18}O_6$: OMe, 41·9%).

Fraction 4. The syrup (0·24 g.) was shown chromatographically to contain a mixture of 2 : 3 : 6- and 2 : 4 : 6-tri-*O*-methylglucose.

Fraction 5. The syrup (0·78 g.) crystallised and chromatographic examination showed the presence of 2 : 4 : 6-tri-*O*-methylglucose together with some 2 : 3 : 6-tri-*O*-methylglucose. Three recrystallisations from dry ether gave 2 : 4 : 6-tri-*O*-methyl-D-glucose, m. p. and mixed m. p. 120—122°, $[\alpha]_D^{15}$ +73° (equil.) (*c*, 2·0 in H_2O). The identity of the sugars was confirmed by conversion into 2 : 4 : 6-tri-*O*-methyl-*N*-phenyl-D-glucosylamine, m. p. and mixed m. p. 162—164°.

Fraction 6. After separation of fraction 5 the column was eluted with butanol, partly saturated with water, to give a syrup (11 mg.) which travelled on the chromatogram at the rate of a di-*O*-methylglucose.

Estimation of the Relative Proportions of Tri-O-methylglucoses.—A sample (*ca.* 100 mg.) of the hydrolysate of the methylated glucosan was rehydrolysed with 2% hydrochloric acid (15 c.c.) for 4 hr. on the water-bath. After neutralisation of the hydrolysate with silver carbonate, concentration gave a syrup which showed $[\alpha]_D^{16}$ +61° ⟶ +15° (*c*, 0·87 in methanolic 1% hydrogen chloride).

The authors thank Professor E. L. Hirst, F.R.S., for his interest and advice, Professor I. A. Preece and Dr. K. G. Mackenzie for the supply of barley glucosans, and the University of Edinburgh for the award of a Post-graduate Studentship to one of them (R. G. J. T.).

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF EDINBURGH. [*Received, June 3rd,* 1954.]

The Alkaloids of Picralima nitida, *Stapf, Th. and H. Durand. Part II.* Some Investigations concerning the Structure of* pseudo*Akuammigine.*

By SIR ROBERT ROBINSON and A. F. THOMAS.

[Reprint Order No. 5447.]

The spectrographic properties of *pseudo*akuammigine, $C_{22}H_{26}O_3N_2$, from *Picralima nitida*, Stapf, indicate that it is a dihydroindole containing an ester group, $\cdot CO_2Me$. The latter has been reduced to $\cdot CH_2\cdot OH$ affording *pseudo*akuammigol, $C_{21}H_{26}O_2N_2,H_2O$. Nitration of *pseudo*akuammigine gives a nitro-compound, and nitrosation a green *C*-nitroso-compound. The best reconciliation of the somewhat conflicting evidence is obtained on the assumption that $\cdot CO_2Me$ is so close to N(*a*) that it can neutralise the normal activation of the benzene ring by the substituted amino-group. This theory is exemplified in a formula that also takes into account the nature of the congeners of the alkaloid.

*pseudo*AKUAMMIGINE AND AKUAMMICINE HYDROCHLORIDES are obtained together on extraction of the crude alkaloid from *Picralima nitida* seeds with N-hydrochloric acid (cf. Henry, *J.*, 1932, 2759). A 50% mixture of the two alkaloids is often obtained as a well-defined crystalline substance with a sharp melting point, and it is best separated into its components by extraction of a benzene or chloroform solution with the amount of 0·1N-hydrochloric acid required to combine with all the akuammicine, this being slightly the stronger base and having a less soluble hydrochloride. The separation is conveniently followed by

* Part I, *J.*, 1954, 3479.

means of the optical rotation, which is −746° for akuammicine, and −35° for *pseudo*-akuammigine. The later fractions of the hydrochloric acid extraction of the crude base give a mixture of akuammigine and *pseudo*akuammigine, separated by the sparing solubility of akuammigine hydrochloride in water. The *pseudo*akuammigine is then easily purified through the hydriodide (cf. Henry, *loc. cit.*).

*pseudo*Akuammigine has the formula $C_{22}H_{26}O_3N_2$, containing one methoxyl, one methylimino-, and one *C*-methyl group. At first, it was believed that two of the latter groups were present (Millson, Robinson, and Thomas, *Experientia*, 1953, **9**, 89), but further analyses have not confirmed this, and Kuhn–Roth estimations in this group of alkaloids have been shown to be unreliable (Robinson and Thomas, Part I). The ultra-violet absorption spectrum is that of a dihydroindole (Raymond-Hamet, *Compt. rend.*, 1950, **230**, 1183), although the curve is not quite coincident with that of ajmaline (Anet, Chakravarti, Robinson, and Schlittler, *J.*, 1954, 1242).

The colour reactions of *pseudo*akuammigine are different from those of ajmaline or strychnidine. Thus nitric acid gives a brownish-yellow colour (Henry, *loc. cit.*); ferric chloride gives a feeble red colour only on warming, and no coupling to an azo-compound occurs with diazotised sulphanilic acid in acetic acid solution—very slow coupling occurs, however, in the presence of sodium acetate in *dilute* acetic acid. The basic strength of *pseudo*akuammigine is nearer to that of strychnine than that of strychnidine (cf. Prelog and Häfliger, *Helv. Chim. Acta*, 1949, **32**, 1851).

The infra-red spectrum of *pseudo*akuammigine shows that no NH or OH group is present; bands corresponding to C=O (probably in a saturated ester) and a 1 : 2-disubstituted benzene ring are observed.

The evidence of the failure of colour reactions suggests that the group :N(*a*)·CO· is present but the spectra do not support this hypothesis. Nitration and nitrosation occur readily, the nitroso-compound having the green colour characteristic of di-*N*-substituted *p*-nitroso-anilines. After reduction of the nitroso-compound, the product gives a blood-red colour with nitric acid, similar to that observed with akuammine (Henry and Sharp, *J.*, 1927, 1950).

Reduction of *pseudo*akuammigine with lithium aluminium hydride in ether gives the corresponding alcohol, *pseudo*akuammigol, confirming the presence of a methyl ester group in the alkaloid. *pseudo*Akuammigol gives the colour reactions of strychnidine, although the ferric chloride coloration is still reluctant. The ultra-violet spectrum is now identical with that of ajmaline.

*pseudo*Akuammigine could not be hydrolysed to a corresponding acid by 7 hours' boiling with aqueous-alcoholic 10% potassium hydroxide.

Neither *pseudo*akuammigine nor *pseudo*akuammigol could be reduced catalytically: indeed the only reason for assuming the presence of a double bond is the composition of the base. The formula $C_{22}H_{28}O_3N_2$ is not excluded by the analyses but $C_{22}H_{26}O_3N_2$ gives the better fit for the derivatives. Naturally it is possible that *pseudo*akuammigine is heptacyclic. However, it is very likely that the phenolic base, akuammine, is hydroxy*pseudo*akuammigine since, apart from the band due to hydroxyl, the infra-red spectra are very similar (Millson, Robinson, and Thomas, *loc. cit.*). In the case of akuammine the H_{26} formula was found much the better (*idem, ibid.*) and there was some evidence of catalytic hydrogenation.

The amount of *pseudo*akuammigine available has been very small and this precluded attempted degradation on the required scale.

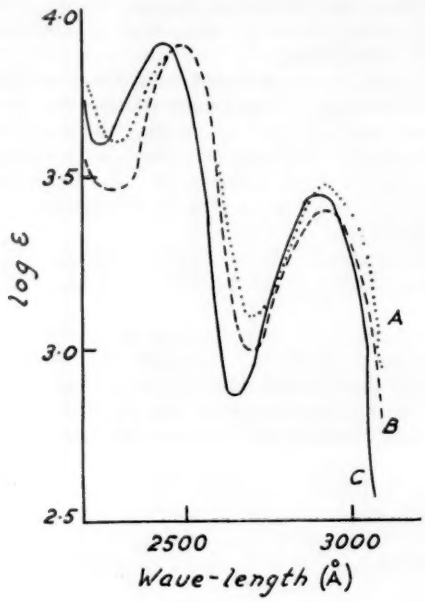
On the assumption of the suggested relation to akuammine we may take cognisance of the formation of 3-ethylpyridine from that base (*idem, ibid.*). Moreover akuammigine (Part I) affords alstyrine, and *pseudo*akuammigine contains a third oxygen atom which is present neither in a carbonyl nor in a hydroxyl group, and must be in a cyclic ether group.

These facts lead to the conclusion that the alkaloid is the result of a Woodward fission at some stage. But as it appears to be a dihydro-indole (ultra-violet spectrum) the simplest working hypothesis, and it is no more than this, can be based on the β-indole-alkaloid type.

The remarkable deactivation of the position *para* to N(*a*) cannot be due to the presence of :N(*a*)·CO· because (1) the ultra-violet spectrum would then be quite different from that

observed, and (2) the infra-red band for :N·CO· should be noted, but is absent, and (3) the green nitroso-compound would not be formed. The deactivation may plausibly be regarded as due to neutralisation of a potentially basic, anionoid N(*a*) across space, and the only available group that could effect this is the carbonyl of ·CO_2Me (cf. Anet, Bailey, and Robinson, *Chem. and Ind.*, 1953, 944).

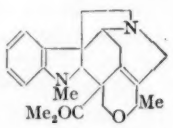
The formula suggested by Millson, Robinson, and Thomas (*loc. cit.*) is based on the arrangement of groups in yohimbine moved round one place clockwise so as to give a β-indole alkaloid instead of the α-type (yohimbine, corynantheine, akuammigine). However the proposed position of the double bond became untenable when Bader (*Helv. Chim. Acta*,

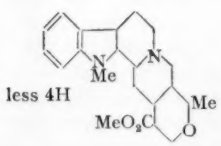


A, ..., pseudo*Akuammigol*.
B, – – – –, *Ajmaline*.
C, ———, pseudo*Akuammigine*.

1953, **36**, 215) found that substituted vinyl ethers show strong absorption in the region near 6·05 μ. This is not noted in the infra-red spectra of *pseudo*akuammigine and akuammine. Hence the small modification to (I) is necessary.

(I)





(II)

In order that the foregoing argument may be better understood we append the α-type structure (II) related to (I). Here the ester group is surprisingly more remote from N(*a*) than in (I); moreover αβ-disubstituted dihydroindoles have not yet been found among plant products.

The field of discussion is clearly widened considerably if we move the ester group from the yohimbine–corynantheine position, but there is no advantage to be gained by following this line of argument at the present stage. The structure (I) appears to present the greatest common measure of compliance with the requirements at this juncture and it is tentatively proposed as a basis for discussion.

Experimental

Fractional extraction of the crude alkaloid with N-hydrochloric acid gave a mixture of akuammicine and *pseudo*akuammigine (cf. Henry, *loc. cit.*), from which a crystalline perchlorate was obtained. This was recrystallised twice from water, then basified, and the base recrystallised from aqueous ethanol, glistening plates, m. p. 147—148°, $[\alpha]_D^{19}$ −347° (*c* 0·98 in EtOH), being obtained, corresponding to a mixture of akuammicine and *pseudo*akuammigine in nearly equimolecular proportion. The infra-red spectrum of this material showed sharp peaks due to the separate absorption by each alkaloid. Attempted separation by recrystallisation of the hydrobromides, perchlorates, and oxalates was unsuccessful. The solution of the mixture in chloroform was shaken with the quantity of 0·1N-hydrochloric acid found to be required to remove all the akuammicine, the organic solution was well washed with water (akuammicine hydrochloride being slightly soluble in chloroform), and the liberated bases recrystallised from aqueous ethanol. This gave, from the aqueous phase, akuammicine (88% pure; m. p. 166—168°, $[\alpha]_D^{18}$ −660°), and, from the organic phase, *pseudo*akuammigine (95% pure; m. p. 158°, $[\alpha]_D^{19}$ −56°). Recrystallisation of *pseudo*akuammigine to constant rotation from aqueous ethanol gave the pure base as colourless, square plates, or from benzene–light petroleum as thick prisms, m. p. 165°, $[\alpha]_D^{18}$ −35° (*c* 1·2 in EtOH), pK_a 7·35 (Found: C, 72·2; H, 7·2; N, 7·3; OMe, 9·8; NMe, 5·0; *C*-Me, 5·9, 5·8, 4·1; active H, 0·0. Calc. for $C_{22}H_{26}O_3N_2$: C, 72·1; H, 7·2; N, 7·6; OMe, 8·5; NMe, 7·9; *C*-Me, 4·1%).

The solution of the hydrochloride obtained from the later fractions of the extraction was heated to boiling, and a hot strong solution of potassium iodide was added. *pseudo*Akuammigine hydriodide crystallised gradually and separated from aqueous acetone containing a trace of sodium dithionite as lustrous colourless needles, m. p. 216° (decomp.), $[\alpha]_D^{19}$ −9° (*c* 1·4 in EtOH), −4° (*c* 1·8 in acetone). The salt was difficult to dry: after 5 hours at 100°/0·005 mm. about 0·5H_2O is still present (Found: C, 52·4, 52·5; H, 5·8, 5·9; I, 24·0, 26·3; OMe, 6·2; NMe, 5·8. Calc. for $C_{22}H_{26}O_3N_2,HI,\frac{1}{2}H_2O$: C, 52·5; H, 5·6; I, 25·3; OMe, 6·2; NMe, 5·8%).

*pseudo*Akuammigine hydrochloride crystallised from water or ethanol as colourless, flat needles, m. p. 215—220° (decomp.), $[\alpha]_D^{19}$ −23° (*c* 1·2 in EtOH) (Found: loss at 100°, 4·2; C, 62·8; H, 6·7; N, 6·7; Cl, 8·3; *C*-Me, 3·5. Calc. for $C_{22}H_{26}O_3N_2,HCl,H_2O$: C, 62·8; H, 6·5; N, 6·7; Cl, 8·4; *C*-Me, 3·6; 1H_2O, 4·3. Found, in anhydrous material: C, 65·3; H, 6·7; N, 7·0. Calc. for $C_{22}H_{26}O_3N_2,HCl$: C, 65·7; H, 6·7; N, 7·0%).

pseudo*Akuammigine hydrobromide*, made from the hydrochloride by addition of aqueous potassium bromide, crystallised from water as clusters of needles having a trace of colour that was difficult to remove. The salt had m. p. 185°, $[\alpha]_D^{19}$ −23° (Found: C, 56·7; H, 6·2; N, 5·7; Br, 17·5. $C_{22}H_{26}O_3N_2,HBr,H_2O$ requires C, 56·7; H, 6·3; N, 6·0; Br, 17·2%).

The *perchlorate* formed colourless needles (from water), m. p. 196° (Found: C, 56·5; H, 5·8; N, 6·3; Cl, 7·7. $C_{22}H_{26}O_3N_2,HClO_4$ requires C, 56·6; H, 5·8; N, 6·0; Cl, 7·6%).

The *oxalate* formed long plates (from water), m. p. 166° (Found: C, 60·5; H, 5·7; N, 5·8. $C_{22}H_{26}O_3N_2,C_2H_2O_4,H_2O$ requires C, 61·0; H, 6·1; N, 5·9%).

Attempted Catalytic Reduction of pseudo*Akuammigine*.—A solution of *pseudo*akuammigine (210 mg.) in ethanol (30 c.c.), with 10% palladised charcoal (50 mg.), was shaken under hydrogen. No significant absorption took place in 2 hr. With Adams catalyst in acetic acid (60%; 30 c.c.), a very slow uptake of hydrogen occurred; after 48 hr., a gum was isolated by filtration and basification, which, after recrystallisation from aqueous ethanol, had m. p. 162° and gave a bright red colour with concentrated nitric acid. Two further recrystallisations from the same solvent gave *pseudo*akuammigine, m. p. and mixed m. p. 164°.

Attempted Hydrolysis of pseudo*Akuammigine*.—The alkaloid (115 mg.) was heated under reflux for 7 hr. with ethanolic potassium hydroxide (15 c.c. of 10%). Concentration and dilution gave *pseudo*akuammigine (105 mg.), m. p. undepressed by an authentic sample.

Reduction of pseudo*Akuammigine with Lithium Aluminium Hydride*.—The alkaloid (1·8 g.) in ether (100 c.c.) was treated with lithium aluminium hydride (0·4 g.) in ether. After 2 hr. the excess of hydride was decomposed with a little water and the precipitated hydroxides were removed by filtration, the residue being washed with chloroform. Evaporation of the solvent gave a glass which crystallised when rubbed with ether–chloroform. Recrystallisation from the same solvent afforded colourless needles of *pseudo*akuammigol, m. p. 201°, $[\alpha]_D^{18}$ −174° (*c*, 2·3 in EtOH), pK_a 8·22. The base could not be obtained anhydrous without decomposition. After drying at 100°/0·01 mm. for 3 hr., the *monohydrate* was obtained (Found: C, 71·2; H, 8·1; N, 7·5. $C_{21}H_{26}O_2N_2,H_2O$ requires C, 70·9; H, 7·9; N, 7·8%).

The *hydrochloride* separated from ethanol, in which it is sparingly soluble in the cold, as

colourless stumpy needles, m. p. 282—284° (decomp.) (Found, in air-dried material: loss at 120°/0·002 mm. in 15 hr., 2·5; C, 63·9; H, 8·0; OMe, 4·6; NMe, 5·6 $C_{21}H_{26}O_2N_2,HCl,H_2O$ requires C, 64·1; H, 7·4; OMe, 7·9; NMe, 7·4; H_2O, 2·3%. Found, in dried material: C, 65·7; H, 7·7; N, 7·6; Cl, 9·7. $C_{21}H_{26}O_2N_2,HCl,\frac{1}{2}H_2O$ requires C, 65·7; H, 7·4; N, 7·3; Cl, 9·7%). This hydrochloride coupled slowly with diazobenzenesulphonic acid in aqueous acetic acid in the presence of sodium acetate. The brownish-yellow solution became crimson on the addition of hydrochloric acid.

The *perchlorate* crystallised from water as lustrous needles, m. p. 258—262° (decomp.) (Found, in material dried for 12 hr. at 100° *in vacuo*: C, 57·2; H, 6·6; N, 6·1; Cl, 7·7. $C_{21}H_{26}O_2N_2,HClO_4$ requires C, 57·5; H, 6·2; N, 6·4; Cl, 8·1%).

There was no significant uptake of hydrogen on shaking a methanol solution of the base with Adams catalyst of known activity under hydrogen for 2 hr.

By the procedure employed in the reduction of akuammigine (Part I) with sodium and liquid ammonia in the presence of ethanol, *pseudo*akuammigine gave a red tar from which no crystalline product was isolated. *pseudo*Akuammigol gave a similar result: a small amount of *pseudo*-akuammigol hydrochloride was recovered.

Nitrosation of pseudo*Akuammigine*.—Sodium nitrite (0·3 g.) in water (5 c.c.) was added to a stirred solution of *pseudo*akuammigine (1·2 g.) in concentrated hydrochloric acid (15 c.c.) and water (15 c.c.) below 5°. The resulting red-brown solution was kept at 0° for 5 min., then diluted with an equal volume of water and neutralised rapidly with ammonia (*d* 0·88) and ice. Isolation of the product with ether, and recrystallisation from ether–light petroleum (b. p. 40—60°), gave bright green rods of *nitroso*pseudo*akuammigine*, m. p. 204° (decomp. to red liquid) (0·8 g.) (Found: C, 66·8; H, 6·4; N, 10·8. $C_{22}H_{25}O_4N_3$ requires C, 66·8; H, 6·4; N, 10·6%).

Nitroso*pseudo*akuammigine absorbed 2 mols. of hydrogen in 30 min. when shaken in methanol with 10% palladised charcoal under hydrogen (microhydrogenation apparatus). The product oxidised rapidly in methanol solution in air, and gave a bright red colour with concentrated nitric acid.

Nitration of pseudo*Akuammigine*.—*pseudo*Akuammigine (0·5 g.) was added portionwise to a mixture of concentrated nitric acid (10 c.c.) and water (10 c.c.) at 0°. The yellow solution was allowed to reach the toom temperature during 5 min., the colour deepening; if allowed to stand too long, the solution became brown and the yield was considerably lower. The solution was basified with ammonia and the yellow *nitro*pseudo*akuammigine* was collected. After recrystallisation (with difficulty) from ether–light petroleum (as rods) or from aqueous acetone (as rectangular plates), the nitro-compound had m. p. 210° (decomp.). The crude product was often contaminated with a brown sludge, but was easily separated by dissolution in acetone in which the impurity was insoluble (Found: C, 64·3; H, 6·1; N, 10·1. $C_{22}H_{25}O_5N_3$ requires C, 64·2; H, 6·1; N, 10·2%).

Infra-red data (*Nujol suspensions*).—*pseudo*Akuammigine: 5·76 [C=O (unconjugated ester)], 6·23 [C=C (aromatic)], and 13·26 μ (1 : 2-disubstituted benzene ring). *pseudo*Akuammigol hydrochloride: many bands in OH and NH stretching region; 6·25 [C=C (aromatic)] and 13·34 μ (1 : 2-disubstituted benzene ring). Except for the absence of bands at 3·06 μ (OH) and at 12·33 μ (1 : 2 : 4-trisubstituted benzene) the curve for *pseudo*akuammigine closely resembles that observed for akuammine.

The authors are grateful to the D.S.I.R. for a maintenance grant to one of them (A. F. T.) and to Sir John Simonsen, F.R.S., and Dr. R. A. E. Galley, Directors of Colonial Products Research, for kindly arranging the collection of seeds of *Picralima nitida* in W. Africa.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, June 8th*, 1954.]

α-1 : 4-*Glucosans. Part II.* The Molecular Structure of the Liver Glycogen from a Case of von Gierke's Disease.*

By D. J. Manners.

[Reprint Order No. 5375.]

The liver glycogen isolated from a case of von Gierke's disease has a chain length of 6 glucose residues, a molecular weight of ~10^3, and a β-amylolysis limit of 14%. Its $[\alpha]_D$ is +201° and it gives no colour with iodine. The glycogen is degraded by salivary α-amylase and is not attacked by muscle phosphorylase. The molecular structure resembles that of a phosphorylase limit-dextrin of a normal glycogen, but differs in having shorter exterior chains.

Von Gierke's or glycogen-storage disease is a metabolic disorder which is accompanied by the deposition of unusually large amounts of glycogen in the liver, skeletal muscle, and other tissues. Illingworth and Cori (*J. Biol. Chem.*, 1952, **199**, 653) isolated glycogen from the livers of ten cases of von Gierke's disease. Structural studies (by enzymic methods; cf. Cori and Larner, *ibid.*, 1951, **188**, 17; Larner, Illingworth, Cori, and Cori, *ibid.*, 1952, **199**, 641) showed that eight of these glycogens had structures similar to those of other mammalian glycogens, *viz.*, unit chains of 11—13 glucose residues, phosphorolysis limits of 33—42%, and absorption maxima of the iodine complexes at 470 mμ. In the ninth case, glycogen was obtained from both liver and muscle tissues which had shorter unit chains and was only slightly degraded by muscle phosphorylase (see Table 1). The tenth glycogen superficially resembled an amylopectin since the unit chains comprised 21 glucose residues, and were degraded 51% by phosphorylase, whilst the "glycogen"–iodine complex had an absorption maximum at 530 mμ. No estimate of the degree of multiple branching in these glycogens was recorded (cf. Hirst and Manners, *Chem. and Ind.*, 1954, 224). Polglase, Smith, and Tyler (*J. Biol. Chem.*, 1952, **199**, 97) examined glycogen obtained from two cases of von Gierke's desease: in one case the liver glycogen had a normal chain length; in the second the unit chains of the liver glycogen were *ca.* 25% shorter, whilst the muscle glycogen appeared to be normal. Sedimentation studies were also carried out on these glycogens (Polglase, Brown, and Smith, *ibid.*, p. 105; see Table 2). The present paper is concerned with the molecular structure of a von Gierke liver glycogen which was found to be different from those described above.

The liver, obtained at autopsy, was kindly placed at our disposal by Professor H. A. Krebs, F.R.S. Glycogen was isolated from the tissue by repeated extraction with hot water; the aqueous extracts were freed from protein by 4% trichloroacetic acid, and the glycogen was precipitated with ethanol and further purified by precipitation with 80% acetic acid (Bell and Young, *Biochem. J.*, 1934, **28**, 882). The purified glycogen dissolved in water ($[\alpha]_D$ +201°) to give an opalescent solution which, unlike that of other glycogens, was not stained brown with iodine. Quantitative measurements of the iodine-binding power by potentiometric titration (Anderson and Greenwood, *Chem. and Ind.*, 1953, 642) showed a much lower binding power than that of normal glycogens (Greenwood and Manners, unpublished work). Acid hydrolysis of the glycogen gave glucose and no other reducing sugar. Salivary amylolysis of the glycogen caused rapid breakdown to reducing sugars (maltose and higher oligosaccharides), showing the presence of α-1 : 4-glucosidic linkages. The absence of maltulose in the α-amylolytic digest indicates that fructose is absent in the original polysaccharide (cf. Peat, Roberts, and Whelan, *Biochem. J.*, 1952, **51**, xvii). End-group assay by potassium periodate (Bell and Manners, *J.*, 1952, **3641**; Halsall, Hirst, and Jones, *J.*, 1947, 1399) showed that the unit chains contain, on the average, 6 glucose residues. This low value was not due to impurities of low molecular weight or to degradation products since the chain length was unaltered after prolonged dialysis of the glycogen. In an attempt to detect the presence of glucosidic linkages

* Part I, *J.*, 1954, 1891.

other than 1 : 4 or 1 : 6, a sample of periodate-oxidised glycogen was hydrolysed with acid, and the hydrolysate examined for glucose (cf. Hirst, Jones, and Roudier, *J.*, 1948, 1779; Part I, *loc. cit.*). No glucose could be detected (by paper chromatography) in the hydrolysate; 1 : 2- and 1 : 3-glucosidic linkages are therefore not present in the von Gierke glycogen. Treatment of the glycogen with a solution of crystalline sweet potato β-amylase resulted in a 14% conversion into maltose. The glycogen was not appreciably attacked by muscle phosphorylase in the presence of an excess of inorganic phosphate. Ultra-centrifugal examination of the glycogen, by Dr. C. T. Greenwood, showed that the glycogen was polydisperse and contained two components; the major component sedimented at 48 *S* * and the minor component at 200 *S* [equivalent to molecular weights of *ca.* 2 and 9 × 10^6 respectively, on the assumption that the diffusion constant is similar to that of rabbit-liver glycogen (see Bell, Gutfreund, Cecil, and Ogston, *Biochem. J.*, 1948, **42**, 405)]. The von Gierke glycogen is therefore a highly branched α-1 : 4-glucosan, composed of *ca.* 10^3 unit chains—each comprising, on the average, 6 glucose residues—which are interlinked only by 1 : 6-glucosidic linkages.

These results suggest that the von Gierke glycogen *qualitatively* resembles the phosphorylase limit-dextrin of a normal glycogen. Such a dextrin would have short unit chains and a low β-amylolysis limit [that of a normal glycogen is *ca.* 45% (Bell and Manners, *loc. cit.*)], and be resistant to attack by muscle phosphorylase. However, from a consideration of the action pattern of β-amylase and muscle phosphorylase, it will be shown that the von Gierke glycogen is not *identical* with a normal phosphorylase limit-dextrin.

Branched α-1 : 4-glucosans contain three types of unit chain; all three are linear chains of α-1 : 4-linked glucose residues, but they differ in the position of the linkage(s) to adjacent chains (Peat, Whelan, and Thomas, *J.*, 1952, 4546), *viz.*: A-chain, joined to the rest of the molecule only by a single glucosidic linkage from the reducing group; B-chain, joined to the molecule by its reducing group and one or more linkages involving $C_{(6)}$ of constituent glucose residues; C-chain, the sole chain in the molecule which is terminated by a free reducing group. An A-chain corresponds to a "side-chain," and a B-chain to a "main-chain" in the terminology of Cori and Larner (*loc. cit.*). Muscle phosphorylase has a different affinity for A- and B-chains; Cori and Larner (*loc. cit.*) have shown that in a phosphorylase limit-dextrin, the A-chain contains only one glucose residue whilst the exterior portion of the B-chain probably comprises 5 or 6 glucose residues (assuming that the dextrin contains equal numbers of A- and B-chains). This dextrin has a β-amylolysis limit of 24% (Hestrin, *J. Biol. Chem.*, 1949, **179**, 943), equivalent to the loss of one maltose residue per unit chain, enzyme action being limited to the B-chains from which two maltose residues are removed. The von Gierke glycogen thus differs from a phosphorylase limit-dextrin, since the β-amylolysis limit is only 14%. This figure represents the loss of *ca.* one glucose residue per chain, equivalent to the loss of one maltose residue from only half of the chains. The average exterior chain length of the von Gierke glycogen is therefore approximately half that of a normal phosphorylase limit-dextrin, *i.e.*, two glucose units. The interior chains of the von Gierke glycogen thus comprise three glucose residues. The low β-amylolysis limit obtained in the present study suggests either that the glycogen contains a relatively small proportion of B-chains (*i.e.*, a high degree of multiple branching) or that, *in vivo*, muscle phosphorylase has a higher affinity for the glucosidic linkages in B-chains than *in vitro*. The former possibility is now being investigated.

The occurrence of a glycogen with short unit chains of *ca.* 6 glucose residues is unusual, but not unique. Certain samples of glycogen from *Mytilus edulis* and *Helix pomatia* have chain lengths of *ca.* 5 and 7 glucose residues, respectively (Bell and Manners, *loc. cit.*), whilst Illingworth, Larner, and Cori (*J. Biol. Chem.*, 1952, **199**, 631) reported that a specimen of tubercle bacillus glycogen had an apparent end-group value of 16% (equivalent to a chain length of *ca.* 6). The last glycogen was not attacked by phosphorylase, and appears to be a phosphorylase limit-dextrin, unlike the short-chain invertebrate glycogens

* Sedimentation constants (S_{20}) are given in Svedberg units where $S = 1 \times 10^{-13}$ c.g.s. units.

which are partially degraded by phosphorylase and have β-amylolysis limits of 41 and 37% respectively. These invertebrate glycogens therefore differ from the von Gierke glycogen in having longer exterior chains and shorter interior chains, even though the constituent unit chains, on the average, are of approximately similar lengths.

The present sample of von Gierke glycogen differs from those examined by Illingworth and Cori and by Polglase *et al.* (*locc. cit.*) as shown in Tables 1 and 2.

TABLE 1. *Action of muscle phosphorylase on von Gierke glycogens.*

Sample	Source	Chain length	Conversion into glucose-1 phosphate (%)
Illingworth and Cori (*loc. cit.*)			
Case no. 1	Liver	12—13	36
Case no. 9	Liver	9	12
	Muscle	7—8	3
Case no. 10	Liver	21	51
Present study	Liver	6	1

When a glycogen is found to have a structure different from that in the "normal organism" one must postulate enzymic imbalance, *i.e.*, an abnormally greater or smaller activity in one or more of the several enzymes concerned in the equilibrium, glycogen $\rightleftharpoons$ glucose. The above data suggest that there are different types of glycogen storage disease. Cori and Cori (*ibid.*, p. 661) observed that, in two fatal cases of the disease,

TABLE 2. *Sedimentation constants of von Gierke glycogens.*

Sample	Source	Sedimentation constant (S_{20}) of major component	Sedimentation constant (S_{20}) of minor component
Polglase, Brown, and Smith (*loc. cit.*)	Liver (patient N.D.)	72—74	220
	Liver (patient P.N.)	75	—
	Skeletal muscle (N.D.)	59—67	29—36
	Cardiac muscle (N.D.)	75	38
Present study	Liver	48	200

glucose-6 phosphatase was "practically absent" from the liver tissue, whilst the formation of the amylopectin-like glycogen may have been due to a deficiency in branching enzyme. Although in the present study no biopsy samples were available for estimation of enzymic activity, it seems probable that the abnormal structure was caused, in part, by a deficiency in the debranching enzyme, amylo-1 : 6-glucosidase, thereby preventing complete phosphorolysis of the glycogen.

EXPERIMENTAL

Isolation of Glycogen.—Liver tissue (500 g.; from a 12-year-old female) which had been boiled in water (500 ml.) and stored under toluene (10 ml.) and octyl alcohol (3 ml.) was received from Professor H. A. Krebs. The solid material was strained off, ground with sand, and extracted four times with boiling water (600 ml.). To the combined, cooled, aqueous extracts and washings (3350 ml.), 40% trichloroacetic acid (380 ml.) was added and the mixture stored at 0° for 12 hr. The precipitated protein was removed by filtration through kieselguhr, and 2 vols. of ethanol were added to the filtrate. The precipitated glycogen was further purified by two precipitations from 80% acetic acid (Bell and Young, *loc. cit.*) and six precipitations from ethanol, and then dried *in vacuo* over phosphoric oxide for 4 hr. at 100°. The yield was 5·2 g.

Properties of the Glycogen.—The glycogen had $[\alpha]_D^{18}$ +201° (*c*, 0·68 in H_2O) (Found: N, 0·026%). Hydrolysis with 1·5N-sulphuric acid at 100° for 2 hr. gave glucose and no other sugar (paper chromatography).

Salivary α-Amylolysis of the Glycogen.—Glycogen (169·8 mg.) was incubated with 0·2M-phosphate buffer (pH 7·0; 10 ml.), 3% aqueous sodium chloride (2 ml.), distilled water (30 ml.), and salivary amylase solution (2 ml.) at 37°. Aliquot portions were removed at intervals for examination on a paper chromatogram and for determination of reducing power (as maltose)

by means of the Shaffer–Somogyi reagent (cf. Bell and Manners, *loc. cit.*). The course of hydrolysis was as follows:

Time of incubation (hr.)	0·08	0·33	0·67	2·50	4·00	6·00	24·00
Apparent conversion into maltose (%)	7·2	13·4	17·8	21·7	23·1	24·6	31·0

No further increase in reducing power was observed after 24 hr. The paper chromatograms showed the presence of maltose and higher maltosaccharides. Glucose and maltulose were absent.

Periodate Oxidation of the Glycogen.—Glycogen (235 mg.) was oxidised by a saturated aqueous solution of potassium periodate, as previously described (Bell and Manners, *loc. cit.*):

Time (hr.)	168	265	432	576
Formic acid production (mg.)	8·2	9·8	10·6	10·9

The maximum formic acid titre is equivalent to a chain length of six glucose residues.

Glycogen (3·0 g.) was dialysed against successive changes of distilled water at room temperature for one week, and then isolated by freeze-drying. The dialysate was concentrated *in vacuo* at 45°; no reducing carbohydrates were present (aniline oxalate spray on paper; heating for 5 min. at 110°).

A sample of the dialysed glycogen (165 mg.) was oxidised with potassium periodate solution as above. The maximum yield of formic acid (obtained after *ca.* 400 hr.) was 7·8 mg., again equivalent to a chain length of six glucose residues.

The remaining solutions of periodate-oxidised glycogen from the assays were combined, dialysed, and freeze-dried. Periodate-oxidised glycogen (64 mg.) was hydrolysed with 2N-sulphuric acid (15 ml.) at 100° for 2 hr. The hydrolysate was cooled, neutralised to pH 5·0 (barium hydroxide) and, after removal of barium sulphate, was freeze-dried. This material was suspended in distilled water (1 ml.) and examined on a paper chromatogram No glucose was present, indicating the absence of 1 : 2- and 1 : 3-linkages in the original glycogen.

β-*Amylolysis of the Glycogen.*—Glycogen (14·0 mg.) was incubated with 0·2M-acetate buffer (pH 4·64; 5 ml.), distilled water (10 ml.), and crystalline sweet-potato β-amylase solution (1 ml.). The course of hydrolysis was:

Time of incubation (hr.)	2	24	48
Conversion into maltose (%)	7·7	14·1	14·3

Phosphorolysis of the Glycogen [with A. M. Liddle].—Glycogen (34·3 mg.) was incubated at 35° with 0·4M-phosphate buffer (pH 6·8; 2·5 ml.), adenylic acid (0·5 mg.), phosphorylase solution (0·25 ml.), and distilled water to a total volume of 10 ml. The phosphorylase was prepared in crystalline form from rabbit muscle by Green and Cori's method (*J. Biol. Chem.*, 1943, **151**, 21). Samples (2 ml.) were withdrawn at intervals for estimation of glucose-1 phosphate, a slight modification of Allen's method being used (*Biochem. J.*, 1940, **34**, 858). Enzyme action gave *ca.* 1% conversion into glucose-1 phosphate after 45 hr. Under these conditions, 13-unit fœtal sheep-liver glycogen was degraded as follows:

Time (hr.)	1·3	4·0	25·5	49·5
Conversion into glucose-1 phosphate (%)	19	21	23	23

The author is indebted to Professor E. L. Hirst, F.R.S., and Dr. D. J. Bell for their interest in this work, and to Dr. C. T. Greenwood for the determination of the sedimentation constants of the glycogen.

Department of Chemistry, University of Edinburgh. [*Received, May 7th*, 1954.]

Bisbenzylisoquinolines. Part I. The Synthesis of 4-(2-Aminoethyl)-5′-carboxymethyl-2 : 2′-dimethoxydiphenyl Ether and Phenoxyisoquinolines.

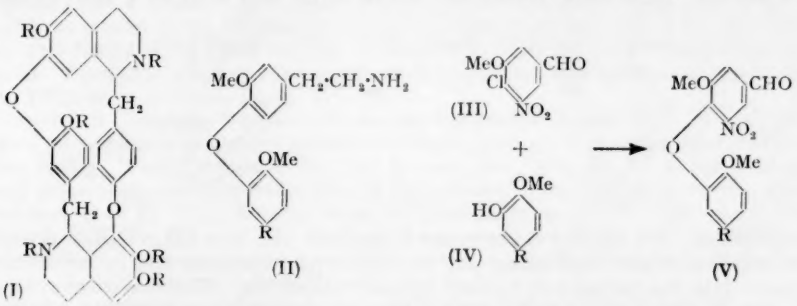
By M. F. GRUNDON and (in part) H. J. H. PERRY.

[Reprint Order No. 5376.]

Formyldiphenyl ethers of type (V) have been prepared from 4-chloro-3-methoxy-5-nitrobenzaldehyde and the appropriate phenols, and converted into the 2-phenylethylamines (II). The amine (II; R = H) gave high yields of phenoxy*iso*quinoline derivatives.

IN spite of the medicinal importance of tubocurarine, a member of the cyclic bisbenzyl-*iso*quinoline group of alkaloids, the synthesis of this type of compound has attracted little interest. Kondo, Katoaka, and Nakagawa (*Ann. Rept. ITSUU Lab.*, 1952, **3**, 49) synthesised cepharanthine, but there is no record of any attempt to prepare bisbenzyl-*iso*quinolines of the general type (I) represented by the alkaloids curine, bebeerine, and the quaternary derivative tubocurarine. We have prepared the amino-acid (II; R = CH_2·CO_2H) and phenoxy*iso*quinoline derivatives which are possible intermediates in such a synthesis, for example, of *OO′*-dimethylcurine (I; R = Me).

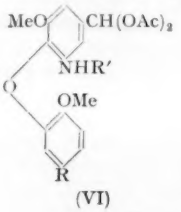
Whaley, Starker, and Meadow (*J. Org. Chem.*, 1953, **18**, 833), during a discussion of a possible synthesis of *iso*tetrandrine, commented on the difficulty of preparing suitable diphenyl ethers by the normal Ullmann procedure, but Borrows, Clayton, Hems, and Long (*J.*, 1949, S 190) showed that chloro-2 : 4-dinitrobenzenes and 2 : 4-dinitrophenyl toluene-*p*-sulphonates readily condense with phenols in pyridine. It now appears that the presence of two nitro-groups is not essential for the success of the method, provided there are present other groups which produce a similar activation. Thus, 4-chloro-3-methoxy-5-nitrobenzaldehyde (III) in pyridine condensed with guaiacol (IV; R = H) or with methyl *iso*vanillate (IV; R = CO_2Me) to give the diphenyl ether derivatives (V; R = H and CO_2Me) in yields of 47% and 63% respectively. 4-Chloro-3-methoxy-5-nitrobenzaldehyde was prepared by heating 5-nitrovanillin with phosphorus oxychloride, toluene,



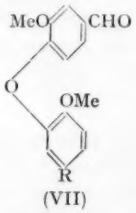
and 1 mol. of diethylaniline. Borrows *et al.* (*loc. cit.*) observed that excess of diethylaniline caused no decrease in yield, but there was such a decrease in the present case. The use of toluene as solvent, instead of the customary large excess of phosphorus oxychloride, proved more convenient for large-scale preparations. The alternative synthesis, employing 5-nitrovanillin toluene-*p*-sulphonate and guaiacol, gave a lower yield (25%) of the diphenyl ether (V; R = H). A similar result was obtained when 5-nitrovanillin was heated in pyridine with toluene-*p*-sulphonyl chloride and guaiacol.

The availability of diphenyl ether derivatives of type (V) suggested a possible synthesis of (II) involving replacement of the nitro-group by hydrogen, and subsequent conversion of the aldehyde into a 2-phenylethylamine derivative. The nitro-aldehyde (V; R = H) was converted into the diacetate, in order to protect the formyl group during the subsequent catalytic reduction. The amine (VI; R = R′ = H) was unstable, but was

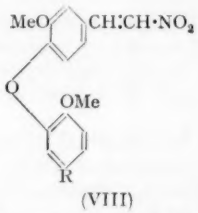
characterised as the triacetate (VI; R = H, R′ = Ac). The amine in acetic acid was diazotized and treated with hypophosphorous acid to give the aldehyde (VII; R = H) in 70% yield, based on the nitro-aldehyde. The β-nitrostyrene derivative (VIII; R = H), prepared from the aldehyde (VII; R = H) in high yield by nitromethane and aqueous alkali, was reduced to the amine (II; R = H) by lithium aluminium hydride (70% yield) or catalytic reduction (60% yield).



(VI)

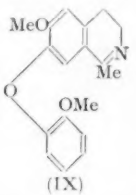


(VII)

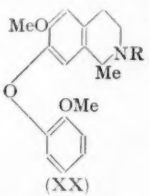


(VIII)

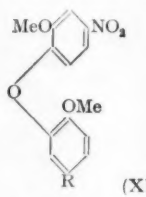
Preparations of 3-hydroxy-4-methoxyphenylacetic acid (IV; R = CH_2·CO_2H) from *iso*vanillin reported by Späth and Lang (*Monatsh.*, 1921, **42**, 273), Hahn and Schulz (*Ber.*, 1939, **72**, 1302) and Bersch (*Arch. Pharm.*, 1939, **277**, 271) gave only 18—40% yield but the rhodanine method (cf. Fischer and Hibbert, *J. Amer. Chem. Soc.*, 1947, **69**, 1208) afforded a 44% yield (H. J. H. Perry). With 4-chloro-3-methoxy-5-nitrobenzaldehyde this acid gave a 48% yield of the formyldiphenyl ether (V; R = CH_2·CO_2Me), the nitro-group in which was replaced as in the earlier case. The intermediate amine (VI; R = CH_2·CO_2Me, R′ = H) was characterised as the triacetate. Partial hydrolysis of the ester group during the reaction resulted in the isolation of some of the aldehydo-acid (VII; R = CH_2·CO_2H), which was conveniently prepared from the ester by hydrolysis with potassium hydrogen carbonate. The ester (VII; R = CH_2·CO_2Me) gave the β-nitrostyrene derivative (VIII; R = CH_2·CO_2Me) in high yield, but hydrolysis of the latter was not satisfactory. Consequently, the β-nitrostyrene acid (VIII; R = CH_2·CO_2H) was prepared directly from the aldehyde-acid (VII; R = CH_2·CO_2H) and then converted into the amino-acid (II; R = CH_2·CO_2H) by catalytic reduction. This compound was obtained as a hydrate, and, after being heated at 135° *in vacuo*, still retained ½ mol. of water of



(IX)



(XX)



(XI)

crystallisation. The validity of the assigned structure (II; R = CH_2·CO_2H) was confirmed by preparation of the *N*-phthaloyl and the *N*-formyl derivative, and by reconversion of the latter into the amino-acid hydrate by acid hydrolysis. The five-stage synthesis of the amino-acid from 4-chloro-3-methoxy-5-nitrobenzaldehyde and methyl 3-hydroxy-4-methoxyphenyl acetate proceeded in an overall yield of 12%.

These 2-phenylethylamines seem suitable for the preparation of phenoxy*iso*quinoline derivatives. The 3 : 4-dihydro*iso*quinoline (IX) was prepared by standard methods from the amine (II; R = H) in 76% yield. Catalytic reduction gave the tetrahydro*iso*quinoline (X; R = H). The dimethyltetrahydro*iso*quinoline (X; R = Me) was obtained by a similar reduction of the 3 : 4-dihydro*iso*quinoline methochloride.

Earlier attempts to synthesise the amino-acid (II; R = CH_2·CO_2H) involved the preparation of diphenyl ethers of type (XI). Borrows *et al.* (*loc. cit.*) noted that mono-nitroaryl halides failed to condense with phenols in pyridine, and, in accordance with these findings, 2-bromo-5-nitroanisole failed to undergo this reaction. The diphenyl ether derivatives (XI; R = H, Me, and Ac) were prepared by fusing 2-bromo-5-nitroanisole with the potassium salts of the appropriate phenols, but the yields were poor.

Experimental

4-Chloro-3-methoxy-5-nitrobenzaldehyde.—Diethylaniline (7·5 g.) was added gradually to a suspension of 5-nitrovanillin (10 g.) in phosphorus oxychloride (20 c.c.) and toluene (20 c.c.), and the mixture was heated under reflux for 20 min. After being cooled, the solution was added to ice and water (300 c.c.), and the mixture extracted with ether (3 × 70 c.c.). The product, obtained by evaporation of the ether solution, was triturated with light petroleum (b. p. 40—60°). Crystallisation of the residue afforded *4-chloro-3-methoxy-5-nitrobenzaldehyde* (4·5 g.; m. p. 112—115°), obtained from aqueous ethanol as colourless needles, m. p. 118—119° (Found: C, 44·6; H, 2·7; N, 6·7. $C_8H_6O_4NCl$ requires C, 44·6; H, 2·7; N, 6·5%).

4-Formyl-2-methoxy-6-nitrophenyl Toluene-p-sulphonate.—A solution of 5-nitrovanillin (1 g.) in acetone (30 c.c.) and water (10 c.c.) containing aqueous sodium hydroxide (3 c.c.; 2N) was treated with toluene-*p*-sulphonyl chloride (1 g.) and kept at room temperature for 12 hr. After evaporation of the acetone and addition of excess of aqueous sodium hydroxide, the precipitate was collected and dissolved in benzene (20 c.c.). The benzene solution was washed with aqueous sodium carbonate, dried, and evaporated. Trituration of the oily residue with ethanol gave the colourless *toluene-p-sulphonate* (0·75 g., 34%), which crystallised from ethanol in plates, m. p. 144—145° (Found: C, 51·4; H, 3·7. $C_{15}H_{13}O_7NS$ requires C, 51·3; H, 3·7%).

4-Formyl-2 : 2′-dimethoxy-6-nitrodiphenyl Ether (V; R = H).—(*a*) A solution of 4-chloro-3-methoxy-5-nitrobenzaldehyde (4·5 g.) and guaiacol (3·5 g.) in pyridine (20 c.c.) was heated under reflux for 1·5 hr. The precipitate obtained by dilution with water (200 c.c.) was collected, and washed with a small quantity of ethanol. The *product* crystallised from ethanol in pale yellow needles (3·0 g., 47%), m. p. 135—138°, raised to 138—139° by recrystallisation from ethanol (Found: C, 59·4; H, 4·1; N, 4·8. $C_{15}H_{13}O_6N$ requires C, 59·4; H, 4·3; N, 4·6%). *2 : 2′-Dimethoxy-4-(2-nitrovinyl)diphenyl ether* was prepared therefrom with nitromethane and dilute potassium hydroxide solution, and crystallised from aqueous acetic acid in yellow rectangular plates, m. p. 194—195° (Found: C, 55·6; H, 4·4; N, 8·1. $C_{16}H_{14}O_7N_2$ requires C, 55·5; H, 4·1; N, 8·1%).

(*b*) 4-Formyl-2-methoxy-6-nitrophenyl toluene-*p*-sulphonate (0·75 g.), guaiacol (0·40 g.), and pyridine (5 c.c.) were heated under reflux for 1 hr. After the addition of water (50 c.c.), the diphenyl ether derivative was collected and crystallised from ethanol (charcoal) in yellow needles (0·15 g., 25%), m. p. 136—138°, alone or mixed with 4-formyl-2 : 2′-dimethoxy-6-nitrodiphenyl ether.

(*c*) 5-Nitrovanillin (1 g.), toluene-*p*-sulphonyl chloride (1 g.), guaiacol (1 g.), and pyridine (15 c.c.) were heated under reflux for 5 hr., and added to water (50 c.c.). The precipitate was filtered off. Crystallisation from ethanol (charcoal) yielded the diphenyl ether as yellow needles (0·25 g., 17%), m. p. and mixed m. p. 137—138°.

4-Formyl-2 : 2′-dimethoxy-5′-methoxycarbonyl-6-nitrodiphenyl Ether (V; R = CO_2Me).—Treatment of 4-chloro-3-methoxy-5-nitrobenzaldehyde (0·50 g.) in pyridine with methyl *iso*-vanillate (0·46 g.) (Faltis, Holzinger, Ita, and Schwarz, *Ber.*, 1941, **74**, 79) as described in the foregoing preparation, and crystallisation of the product from ethanol, gave the required *diphenyl ether* (0·42 g., 63%), forming cream-coloured plates, m. p. 127—128°, from ethanol (Found: C, 56·8; H, 4·3; N, 3·9. $C_{17}H_{15}O_8N$ requires C, 56·5; H, 4·2; N, 3·9%). The *oxime* crystallised from aqueous ethanol in prisms, m. p. 177—178° (Found: C, 54·5; H, 4·4; N, 7·2. $C_{17}H_{16}O_8N_2$ requires C, 54·3; H, 4·3; N, 7·5%).

3-Hydroxy-4-methoxybenzylidenerhodanine.—*iso*Vanillin (20 g.), rhodanine (20 g.), fused sodium acetate (37 g.), and acetic acid (100 c.c.) were heated under reflux for 10 min., and then transferred to a steam-bath. After 2 hr., the solution was cooled, diluted with water (400 c.c.), and kept at 0° for 4 hr. The orange solid (32·6 g., 91%) was collected and washed with water. The *rhodanine* derivative separated from acetone in yellow needles, m. p. 220—221° (Found: C, 49·5; H, 3·1; N, 5·1. $C_{11}H_9O_3NS_2$ requires C, 49·4; H, 3·4; N, 5·2%).

β-(*3-Hydroxy-4-methoxyphenyl*)-α-*thiopropionic Acid.*—The benzylidenerhodanine (32·6 g.) was heated on a steam-bath with aqueous sodium hydroxide (220 c.c.; 15%) for 1 hr. Hydrochloric acid (230 c.c.; 10%) was added to the ice-cold solution, and the buff precipitate of the *thio-acid* (25·9 g., 94%) was collected and washed with water. It crystallised from aqueous methanol in orange prisms, m. p. 158—160° (Found: C, 53·3; H, 4·5. $C_{10}H_{10}O_4S$ requires C, 53·1; H, 4·5%).

3-Acetoxy-4-methoxybenzyl Cyanide.—A solution of hydroxylamine, prepared from aqueous hydroxylamine hydrochloride (32·5 g. in 30 c.c. of water) and alcoholic sodium ethoxide, and

the above thio-acid (32·7 g.) was heated under reflux for 1 hr., then evaporated, and the residue was dissolved in aqueous sodium hydroxide (250 c.c.; 5%). The filtered solution was acidified at 0° with hydrochloric acid (225 c.c.; 10%), and extracted with ethyl acetate (3 × 100 c.c.). By evaporation, and trituration of the residue with light petroleum (b. p. 60—80°), the hydroxyamino-acid was obtained as a buff solid (30 g., 92%), m. p. 137—143°.

The crude product (4·5 g.) in acetic anhydride (12 c.c.) was heated at 50° until a clear solution was obtained, then on a steam-bath until effervescence ceased (5 min.), diluted with water (100 c.c.), and extracted with ether (3 × 30 c.c.). The ether solution was washed with aqueous sodium carbonate, and then with water. Evaporation gave the *cyanide* (2·2 g., 57%), b. p. 119—122°/0·15 mm., which crystallised. A sample separated from light petroleum (b. p. 60—80°) in colourless prisms, m. p. 60—61° (Found: C, 64·6; H, 5·2; N, 7·0. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4; N, 6·8%).

Methyl 3-Hydroxy-4-methoxyphenylacetate.—The cyanide (8·5 g.) in ethanol (60 c.c.) was heated with aqueous potassium hydroxide (12·5 g. in 60 c.c. of water) under reflux for 10 hr. Removal of the ethanol, followed by acidification, yielded 3-hydroxy-4-methoxyphenylacetic acid (6·6 g.) as pale yellow plates, m. p. 126—129°. A further quantity (0·7 g.) was obtained by extraction of the aqueous solution with ether (total yield, 7·3 g., 97%).

Methanol (60 c.c.) containing sulphuric acid (6 c.c.) was added to a solution of the acid (7·3 g.) in methanol (60 c.c.). The solution was heated under reflux for 10 hr., concentrated at room temperature to 20 c.c., diluted with water (200 c.c.), and extracted with ether (4 × 30 c.c.). After the ether solution had been washed, first with water, then with aqueous sodium hydrogen carbonate, and finally with water, evaporation and distillation gave the required *ester* as a colourless oil (6·4 g., 82%), b. p. 102°/0·1 mm. (Found: C, 60·9; H, 6·4. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·2%).

4-Formyl-2 : 2′-dimethoxy-5′-methoxycarbonylmethyl-6-nitrodiphenyl Ether (V; R = $CH_2{\cdot}CO_2Me$).—4-Chloro-3-methoxy-5-nitrobenzaldehyde (6·40 g.), methyl 3-hydroxy-4-methoxyphenylacetate (5·65 g.), and pyridine (50 c.c.) were heated at 120° for 1 hr. Addition of water (200 c.c.) precipitated the *diphenyl ether*, which crystallised from ethanol in plates (4·85 g.), m. p. 113—114°. The aqueous solution was extracted with ether (3 × 40 c.c.), and the ether solution washed successively with water, 10% hydrochloric acid, water, N-sodium hydroxide, and water. Evaporation of the ether solution, and trituration of the residue with ethanol, gave a further quantity of the diphenyl ether (0·18 g.), m. p. 108—111° (total yield, 5·03 g., 48%). A sample crystallised from ethanol in colourless plates, m. p. 114—115° (Found: C, 57·8; H, 4·5; N, 3·8. $C_{18}H_{17}O_8N$ requires C, 57·6; H, 4·6; N, 3·7%).

6-Amino-4-formyl-2 : 2′-dimethoxydiphenyl Ether Triacetate.—4-Formyl-2 : 2′-dimethoxy-6-nitrodiphenyl ether was converted in 94% yield by acetic anhydride containing sulphuric acid into the *diacetate*, plates, m. p. 103—104° (from ethanol) (Found: C, 56·2; H, 4·7; N, 3·5. $C_{19}H_{19}O_9N$ requires C, 56·3; H, 4·7; N, 3·5%).

The diacetate (0·38 g.) in ethyl acetate (20 c.c.) was hydrogenated at atmospheric pressure and at room temperature in the presence of 5% palladium–charcoal (0·5 g.) until 3 mols. of hydrogen were absorbed. The catalyst was removed and the solution evaporated at room temperature. The residue was acetylated with acetic anhydride in the presence of sulphuric acid. Water was added, and the *triacetate* was collected and crystallised from ethanol in colourless prisms (0·23 g.), m. p. 134—136°. It had m. p. 139—140° after recrystallisation from ethanol (Found: C, 60·3; H, 5·7; N, 3·6. $C_{21}H_{23}O_8N$ requires C, 60·4; H, 5·6; N, 3·4%).

4-Formyl-2 : 2′-dimethoxydiphenyl Ether (VII; R = H).—The foregoing diacetate (4·3 g.) was hydrogenated as described above. The crude amine in acetic acid (15 c.c.) was treated with hydrochloric acid (8 c.c.; 15%), and the solution at 0° was diazotised with sodium nitrite (0·85 g.) in water (2 c.c.). After 20 min., ice-cold aqueous hypophosphorous acid (20 c.c.; 30%) was added gradually with stirring. The solution was kept at 0° for 12 hr., diluted with water (200 c.c.), and extracted with ether (3 × 40 c.c.). The ether solution was washed with aqueous sodium hydroxide (2 × 30 c.c.; 10%), and then with water. Evaporation and distillation yielded *4-formyl-2 : 2′-dimethoxydiphenyl ether* as a pale yellow viscous oil (1·9 g., 70%), b. p. 169—173°/0·2 mm. (Found: C, 69·4; H, 5·8. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·5%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in red needles, m. p. 207—209° (Found: C, 57·5; H, 4·3; N, 12·7. $C_{21}H_{18}O_7N_4$ requires C, 57·2; H, 4·2; N, 12·8%).

2 : 2′-Dimethoxy-4-(2-nitrovinyl)diphenyl Ether (VIII; R = H).—A solution of the preceding aldehyde (4·1 g.) in ethanol (20 c.c.) containing nitromethane (2 g.) at 0° was treated gradually with a solution of potassium hydroxide (2·4 g. in 4 c.c. of water and 6 c.c. of methanol). After

10 min., the solution was added to hydrochloric acid (40 c.c.; 15%). The *2-nitrovinyl* derivative was obtained as a yellow solid (4·5 g., 94%), m. p. 89—92°, and separated from ethanol in yellow needles, m. p. 97—98° (Found: C, 64·0; H, 5·1; N, 4·6. $C_{16}H_{15}O_5N$ requires C, 63·8; H, 5·0; N, 4·7%).

4-(2-*Aminoethyl*)-2 : 2′-*dimethoxydiphenyl Ether* (II; R = H).—(*a*) The nitrovinyl derivative (4·25 g.) in ether (250 c.c.) was added to a solution of lithium aluminium hydride (5 g.) in ether (250 c.c.), and the mixture was heated under reflux for 6 hr. Excess of the reagent was decomposed by moist ether, and the addition of aqueous potassium hydroxide (150 c.c., 40%) caused most of the inorganic precipitate to dissolve. The ether layer was separated, and the aqueous solution was extracted with ether (2 × 50 c.c.). Evaporation of the combined ether solutions and distillation yielded the *amine* as a colourless oil (2·65 g., 70%), b. p. 169—171°/0·2 mm. (Found: C, 69·8; H, 6·9; N, 4·9. $C_{16}H_{19}O_3N$ requires C, 70·3; H, 7·0; N, 5·1%). The *phthaloyl* derivative, prepared by heating the amine in acetic acid with phthalic anhydride, crystallised from ethanol in colourless plates, m. p. 156—157° (Found: C, 71·2; H, 5·3. $C_{24}H_{21}O_5N$ requires C, 71·5; H, 5·3%).

(*b*) The nitrovinyl derivative (0·75 g.) in acetic acid (50 c.c.), containing sulphuric acid (1 c.c.), was shaken in hydrogen in the presence of 5% palladium–charcoal (0·5 g.) until hydrogen absorption ceased (4 hr.). The solution was filtered, concentrated to 10 c.c. at 40°, diluted with water (150 c.c.), and extracted with ether (3 portions). The aqueous solution was made alkaline with 10% aqueous sodium hydroxide, and extracted with ether (5 × 30 c.c.). Evaporation of the ether solution yielded a pale yellow oil (0·41 g., 60%), shown to be identical with 4-(2-aminoethyl)-2 : 2′-dimethoxydiphenyl ether by conversion into the same dihydro*iso*quinoline derivative (see below).

3 : 4-*Dihydro*-6-*methoxy*-7-o-*methoxyphenoxy*-1-*methyl*iso*quinoline* (IX).—4-(2-Aminoethyl)-2 : 2′-dimethoxydiphenyl ether (1·10 g.) was treated with acetic anhydride (5 c.c.). After 30 min., water (100 c.c.) was added, and the mixture kept for 1 hr. before extraction with ether (4 × 30 c.c.). The ether solution was washed with aqueous sodium carbonate and water, dried, and distilled. The *N*-acetyl derivative was obtained as a pale yellow oil (1·15 g.).

The *N*-acetyl derivative (1·15 g.) in toluene (5 c.c.) was refluxed for 1 hr. with phosphorus oxychloride (3 c.c.). The solution was evaporated at 50°, and the gum which remained was triturated with light petroleum (b. p. 40—60°). Addition of ethanol (3 c.c.) and hydrochloric acid (0·5 c.c.) precipitated the *dihydro*iso*quinoline hydrochloride* (0·65 g.), m. p. 190—193°. A further quantity (0·44 g.) was obtained by dilution of the ethanol solution with ether. Recrystallisation from ethanol–ether gave the hydrochloride as colourless needles, m. p. 197—198° (decomp.) (Found: C, 61·6; H, 6·4; N, 4·1; After drying at 120° *in vacuo*: C, 64·6; H, 6·1. $C_{18}H_{20}O_3NCl,1H_2O$ requires C, 61·4; H, 6·3; N, 4·0. $C_{18}H_{20}O_3NCl$ requires C, 64·8; H, 6·0%).

The hydrochloride (1·09 g.) in warm water was treated with aqueous sodium hydroxide, and the mixture extracted with ether. Evaporation gave a colourless gum, which dissolved in light petroleum (b. p. 60—80°). The cold solution deposited the *dihydro*iso*quinoline* as colourless prisms [0·93 g., 76% based on 4-(2-aminoethyl)-2 : 2′-dimethoxydiphenyl ether], m. p. 90—92°. A sample, m. p. 91—92°, was prepared by recrystallisation from light petroleum (b. p. 60—80°) (Found: C, 72·6; H, 6·2; N, 4·9. $C_{18}H_{19}O_3N$ requires C, 72·7; H, 6·4; N, 4·7%).

Tetrahydro-6-*methoxy*iso-7-o-*methoxyphenoxy*-1 : 2-*dimethylquinoline* (X; R = Me).—3 : 4-*Dihydro*-6-*methoxy*-7-o-*methoxyphenoxy*-1-*methyl*iso*quinoline methiodide*, prepared with methyl iodide in ethanol at room temperature, crystallised from ethanol in yellow prisms, m. p. 189—190° (Found: C, 51·7; H, 5·0. $C_{19}H_{22}O_3NI$ requires C, 51·9; H, 5·1%).

When passed through a column of ion-exchange resin (Amberlite IRA-400), a solution of the methiodide (0·3 g.) in water became cloudy. The precipitate probably consisted of the anhydro-base. The column was washed with ether (50 c.c.), and the ether solution was shaken with water (20 c.c.) containing hydrochloric acid (1 c.c.). The acid washings were added to the aqueous solution obtained from the column, and the clear acid solution was evaporated to dryness at 40°, leaving the methochloride as a colourless gum.

The crude methochloride in ethanol (20 c.c.), containing hydrochloric acid (0·5 c.c.), was shaken in hydrogen with platinum (0·2 g.), until hydrogen absorption ceased (30 min.). The catalyst was removed and the solution evaporated. A solution of the oily residue in water (20 c.c.) was made alkaline with sodium hydrogen carbonate and extracted with ether (3 × 10 c.c.). Evaporation of the ether left a colourless gum, which, on trituration with light petroleum (b. p. 40—60°), gave the colourless *tetrahydrodimethyl*iso*quinoline* as a colourless

solid (0·12 g., 55%). A sample crystallised from light petroleum (b. p. 40—60°) in large colourless prisms, m. p. 107—109° (Found: C, 72·9; H, 7·1. $C_{19}H_{23}O_3N$ requires C, 72·8; H, 7·4%). The *methiodide* separated from acetone–ether in colourless plates, m. p. 164—165° (Found: C, 52·7; H, 5·4. $C_{20}H_{26}O_3NI$ requires C, 52·8; H, 5·8%).

Tetrahydro-6-methoxy-7-o-methoxyphenoxy-1-methylisoquinoline (X; R = H).—The dihydro-*iso*quinoline hydrochloride (1·05 g.) in ethanol (30 c.c.), containing hydrochloric acid (1 c.c.), was reduced at room temperature and atmospheric pressure in the presence of platinum (0·2 g.). 1 Mol. of hydrogen was absorbed in 45 min. After removal of the catalyst, the ethanol solution was evaporated, and water (50 c.c.) was added. The solution was made alkaline with aqueous sodium hydroxide and extracted with ether (3 × 20 c.c.). Evaporation of the ether gave the *tetrahydroisoquinoline* (0·44 g., 50%), m. p. 101—102°, crystallising from light petroleum (b. p. 60—80°) in colourless prisms, m. p. 103—104° (Found: C, 72·5; H, 7·1. $C_{18}H_{21}O_3N$ requires C, 72·2; H, 7·1%).

6-Amino-4-formyl-2 : 2′-dimethoxy-5′-methoxycarbonylmethyldiphenyl Ether Triacetate (VI; R = $CH_2{\cdot}CO_2Me$, R′ = Ac).—4-Formyl-2 : 2′-dimethoxy-5′-methoxycarbonylmethyl-6-nitrodiphenyl ether with acetic anhydride and sulphuric acid gave the *diacetate* (100% yield), prisms (from ethanol), m. p. 62—64° (Found: C, 55·4; H, 5·0. $C_{22}H_{23}O_{11}N$ requires C, 55·4; H, 4·9%).

The diacetate (0·25 g.) in ethyl acetate (30 c.c.) was shaken in hydrogen with palladised charcoal (0·5 g.; 5%), until hydrogen absorption ceased (3 hr.). Removal of the catalyst, followed by evaporation at room temperature, gave a yellow gum, which was acetylated with acetic anhydride and sulphuric acid. Addition of water to the acetylation mixture precipitated the *triacetate*, crystallising from ethanol in colourless plates (0·14 g.), m. p. 124—125°, raised by recrystallisation from ethanol to 128° (Found: C, 58·9; H, 5·7. $C_{24}H_{27}O_{10}N$ requires C, 58·9; H, 5·6%).

4-Formyl-2 : 2′-dimethoxy-5′-methoxycarbonylmethyldiphenyl Ether (VII; R = $CH_2{\cdot}CO_2Me$).—The foregoing diacetate (4·17 g.) was reduced, as described in the previous experiment. The crude amine in acetic acid (12 c.c.) was diazotised in hydrochloric acid (12 c.c.; 15%) at 0° with sodium nitrite (0·7 g.) in water (3 c.c.). After 20 min., ice-cold hypophosphorous acid (20 c.c.; 30%) was added during 5 min., and the solution was kept at 0° for 12 hr. Addition of water (150 c.c.), extraction with ether (4 × 40 c.c.), washing with water, N-sodium hydroxide (4 × 10 c.c.), and water, evaporation, and distillation gave a pale yellow viscous oil, b. p. 190—195°(bath)/0·008 mm. By trituration with ethanol, *4-formyl-2 : 2′-dimethoxy-5′-methoxycarbonylmethyldiphenyl ether* was obtained as a colourless solid (1·34 g.), separating from ethanol in prisms, m. p. 88—89° (Found: C, 65·3; H, 5·7. $C_{18}H_{18}O_6$ requires C, 65·5; H, 5·6%). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetone–ethanol in red needles, m. p. 162—163° (Found: C, 56·3; H, 4·3; N, 11·3. $C_{24}H_{22}O_9N_4$ requires C, 56·5; H, 4·3; N, 11·0%).

The alkaline washings were acidified with hydrochloric acid and extracted with benzene (3 × 10 c.c.). The benzene solution was shaken with several portions of aqueous sodium hydrogen carbonate, and the combined alkaline solutions were acidified. Extraction with benzene and removal of the solvent gave *5′-carboxymethyl-4-formyl-2 : 2′-dimethoxydiphenyl ether*, obtained from aqueous ethanol as a cream-coloured solid (0·25 g.). The acid recrystallised from aqueous ethanol in rectangular plates, m. p. 125—127° (Found: C, 64·8; H, 5·4. $C_{17}H_{16}O_6$ requires C, 64·6; H, 5·1%). The total yield of ester and acid was 55%.

5′-Carboxymethyl-4-formyl-2 : 2′-dimethoxydiphenyl Ether (VII; R = $CH_2{\cdot}CO_2H$).—The corresponding ester (0·78 g.) in methanol (30 c.c.) was heated with potassium hydrogen carbonate (1·7 g.) in water (8 c.c.) under reflux for 2 hr. After removal of the methanol, the solution was acidified with hydrochloric acid, and the diphenyl ether acid was collected (0·72 g., 96%; m. p. and mixed m. p. 125—126° after recrystallisation from aqueous ethanol).

2 : 2′-Dimethoxy-5′-methoxycarbonylmethyl-4-(2-nitrovinyl)diphenyl Ether (VIII; R = $CH_2{\cdot}CO_2Me$).—By a method similar to that described for the preparation 2 : 2′-dimethoxy-4-(2-nitrovinyl)diphenyl ether, the *2-nitrovinyl* derivative was obtained from 4-formyl-2 : 2′-dimethoxy-5′-methoxycarbonylmethyldiphenyl ether (0·22 g.) as yellow plates (0·20 g., 80%), m. p. 108—109° after crystallisation from ethanol (Found: C, 60·9; H, 5·0. $C_{19}H_{19}O_7N$ requires C, 61·1; H, 5·1%).

5′-Carboxymethyl-2 : 2′-dimethoxy-4-(2-nitrovinyl)diphenyl Ether (VIII; R = $CH_2{\cdot}CO_2H$).—(*a*) A solution of the above nitrovinyl derivative (0·2 g.) in aqueous N-sodium hydroxide (10 c.c.) and ethanol (5 c.c.) was kept at room temperature for 12 hr. The solution was added to hydrochloric acid (20 c.c.; 15%), and the precipitate was collected. Crystallisation from aqueous ethanol gave the *2-nitrovinyl diphenyl ether* (0·09 g.), in yellow plates, m. p. 189—191° (Found: C, 60·3; H, 4·8. $C_{18}H_{17}O_7N$ requires C, 60·2; H, 4·8%).

(*b*) A solution of 5′-carboxymethyl-2 : 2′-dimethoxy-4-formyldiphenyl ether (0·5 g.) in ethanol (4 c.c.) containing nitromethane (0·4 g.) was treated gradually with aqueous potassium hydroxide (4·5 c.c.; 10%). After 15 min. at 0°, the solution was added to hydrochloric acid (15 c.c.; 10%). The precipitate of the nitrovinyl derivative (0·52 g., 91%) was collected. It separated from aqueous ethanol in yellow plates, m. p. and mixed m. p. 187—189°.

4-(2-*Aminoethyl*)-5′-*carboxymethyl*-2 : 2′-*dimethoxydiphenyl Ether* (II; R = CH_2·CO_2H).—5′-Carboxymethyl-2 : 2′-dimethoxy-4-(2-nitrovinyl)diphenyl ether (0·4 g.), suspended in ethyl acetate (25 c.c.), was added to platinium oxide (0·2 g.), which had been pre-reduced in aqueous sulphuric acid (4 c.c.; 10%), and ethyl acetate (5 c.c.). The mixture was shaken with hydrogen at atmospheric pressure and room temperature until absorption ceased (2 hr.). The catalyst was removed and the aqueous layer was separated. The ethyl acetate solution was washed with water (3 × 10 c.c.), and the combined aqueous solutions were passed through a column of ion-exchange resin (Amberlite IR-4B) and evaporated to dryness. The brown gummy residue, dissolved in ethanol (5 c.c.), was kept at room temperature, and 4-(2-*aminoethyl*)-5′-*carboxymethyl*-2 : 2′-*dimethoxydiphenyl ether* slowly separated (0·21 g., 51%). By repeated crystallisation from 90% ethanol, the compound was obtained as a white powder, m. p. 177—178° (Found : C, 61·6; H, 6·3. Found, after heating at 135°/0·1 mm. for 12 hr. : C, 63·7; H, 6·2; N, 4·4. $C_{18}H_{21}O_5N$,lH_2O requires C, 61·9; H, 6·6. $C_{18}H_{21}O_5N$,$\frac{1}{2}H_2O$ requires C, 63·5; H, 6·4; N, 4·1%). The *phthaloyl* derivative, prepared by fusing the amino-acid with phthalic anhydride at 140—150° for 30 min., separated from methanol in colourless plates, m. p. 183—184° (Found : C, 67·6; H, 5·3; N, 3·1. $C_{26}H_{23}O_7N$ requires C, 67·7; H, 5·0; N, 3·0%).

5′-*Carboxymethyl*-4-(2-*formamidoethyl*)-2 : 2′-*dimethoxydiphenyl Ether*.—The amino-acid (50 mg.) in formic acid (1 c.c.) was kept in acetic anhydride (1 c.c.) at 40—50° for 30 min. The solvent was evaporated, and the oily residue treated with water. By extraction with ethyl acetate, a colourless oil was obtained, affording the N-*formyl* derivative (30 mg.), m. p. 130—136°, when triturated with ether. The compound crystallised from ethyl acetate–ether in prisms, m. p. 138—140° (Found : C, 63·3; H, 6·1. $C_{19}H_{21}O_6N$ requires C, 63·5; H, 5·9%).

Hydrolysis of the N-*Formyl Derivative*.—The derivative (40 mg.) in methanolic hydrogen chloride (5 c.c., 2%) was heated on a steam-bath for 30 min. Removal of the methanol and addition of water (2 c.c.) gave a clear solution, which was added to a column of ion-exchange resin (Amberlite IR-4B). Evaporation of the aqueous solution gave a yellow gum, which crystallised from ethanol as a white solid (25 mg.), m. p. 171—173°, alone or mixed with 4-(2-aminoethyl)-5′-carboxymethyl-2 : 2′-dimethoxydiphenyl ether (Found, after heating at 135°/0·1 mm. for 12 hr. : C, 63·7; H, 6·0. Calc. for $C_{18}H_{21}O_5N$,$\frac{1}{2}H_2O$: C, 63·5; H, 6·4%).

2 : 2′-*Dimethoxy*-4-*nitrodiphenyl Ether* (XI; R = H).—The potassium salt of guaiacol (0·35 g.) and 2-bromo-5-nitroanisole (0·5 g.) were heated at 140—150° for 2 hr., then treated with N-sodium hydroxide (20 c.c.), and extracted with ether (4 × 20 c.c.). The ether solution was dried and evaporated, and the residue was distilled in steam, which removed unchanged bromo-compound (0·17 g.). The solid residue crystallised from ethanol, affording the *diphenyl ether* in light brown prisms (0·22 g., 37%), m. p. 89—90° (Found : C, 61·1; H, 4·6; N, 5·3. $C_{14}H_{13}O_5N$ requires C, 60·9; H, 4·7; N, 5·1%).

2 : 2′-*Dimethoxy*-5′-*methyl*-4-*nitrodiphenyl Ether* (XI; R = Me).—Condensation of 2-bromo-5-nitroanisole (2·2 g.) with potassium 2-methoxy-5-methylphenoxide (1·7 g.) (Faltis *et al.*, *loc. cit.*) was carried out as in the previous experiment. The *diphenyl ether* separated from ethanol in yellow prisms (0·71 g., 30%), m. p. 92—93° (Found : C, 62·2; H, 5·4; N, 4·9. $C_{15}H_{15}O_5N$ requires C, 62·3; H, 5·2; N, 4·8%).

5′-*Acetyl*-2 : 2′-*dimethoxy*-4-*nitrodiphenyl Ether* (XI; R = Ac).—2-Bromo-5-nitroanisole (2·3 g.) was added to a mixture of 5-acetylguaiacol monohydrate (1·80 g.) (Coulthard, Marshall, and Pyman, *J.*, 1930, 280) and potassium hydroxide (0·55 g.) at 160°. Heating was continued for 3 hr. Water (50 c.c.) was added to the cooled melt, and the mixture was extracted with ether (5 × 30 c.c.). The ether extract was dried and evaporated, and the residue steam-distilled. The residue was extracted with ether, and evaporation of the ether solution yielded the required *diphenyl ether*, crystallising from ethanol in yellow prisms (0·73 g., 23%), m. p. 120—123°. A sample, m. p. 127—128°, was prepared by recrystallisation from ethanol (Found : C, 60·8; H, 4·7; N, 4·3. $C_{16}H_{15}O_6N$ requires C, 60·6; H, 4·7; N, 4·4%).

This work was carried out during the tenure of an I.C.I. Research Fellowship. Microanalyses were by Mr. J. M. L. Cameron and Miss M. W. Christie.

UNIVERSITY OF GLASGOW. [*Received, May 10th*, 1954.]

Some Applications of Valence-bond Theory to Aromatic Substitution.

By A. L. Green.

[Reprint Order No. 5392.

The electronic effects of substituents on aromatic substitution are described in terms of valence-bond theory. The influence of electron correlation on the transition-state energies for both electrophilic and nucleophilic aromatic substitution is discussed.

The electronic principles governing aromatic substitution, in particular the difference between *ortho-para*-directing and *meta*-directing substituents, have been known for many years, but there still remain several difficulties, among which predominates the problem of *ortho* : *para* ratios.

For dealing with aromatic substitution two general procedures have been employed. In the first of these, the reactivities of different positions are correlated with the charge distribution in the unperturbed molecule, while in the second an attempt is made to calculate the effect of substituents at different positions on the energy of the transition state for the substitution reaction. As Waters (*J.*, 1948, 727) and others have pointed out, the former method takes into account only the mesomeric effects of substituents and not the more important electromeric effects, and for this reason may prove to be unreliable in dealing with minor differences of reactivity.

Several attempts have been made to calculate accurately both charge distributions (Wheland and Pauling, *J. Amer. Chem. Soc.*, 1935, **57**, 2086) and transition-state energies (Wheland, *ibid.*, 1942, **64**, 900; Dewar, *J.*, 1949, 463) by means of the molecular orbital (MO) method. Unfortunately the results obtained depend on the importance attributed to the transmission of inductive effects along the σ carbon–carbon bonds. To obtain general agreement with experiment it is necessary to assume more extensive transmission than is normally regarded as likely (Brown, *Quart. Reviews*, 1952, **6**, 63). It may be that these high inductive effects have to be introduced in order to compensate for deficiencies in the MO technique, notably the neglect of electron correlation.

For this reason it seems worth while to try to apply the valence-bond (VB) theory to the same problem.

In VB theory the structure of any molecule is considered as a resonance hybrid of various simpler structures. The wave function Ψ of the molecule may be written as

$$\Psi = a\psi_1 + b\psi_2 + c\psi_3 + \ldots .$$

where ψ_1, ψ_2 . . . . are the wave functions of the contributing structures. The coefficients a, b, c . . . . (more exactly their squares) are regarded as measuring the importance of each contributing structure in the actual molecule. For numerical calculations the wave functions ψ_1, ψ_2 . . . . are determined by Slater's method (*Phys. Review*, 1931, **38**, 1109) and the total wave function Ψ and hence the coefficients a, b, c . . . . are determined by minimising the energy.

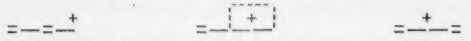
In qualitative resonance arguments it is usual to assume that the importance of any structure is directly related to its energy. This is true where there are two structures only; where there are more than two it is frequently in error (Sherman, *J. Chem. Phys.*, 1934, **2**, 488). The reason why the assumption is successful in practice is that the energy of any structure measures, not its actual importance in the total wave function, but the ease with which the molecule can be polarised into that particular form, and it is this which is usually determined by reactivity experiments. The actual coefficients needed in the calculation of the ground state electronic charge distribution depend, not only on the energy of each structure, but also on the effectiveness with which it interacts with other structures. It is only when these interacting powers are similar that the energies will give a fair measure of the relative importances.

The procedure for the introduction of ionic structures into the VB theory of conjugated systems has been discussed by Craig (*Proc. Roy. Soc.*, 1950, *A*, **200**, 391) and by Schomaker

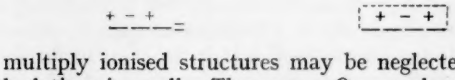
and Simonetta (*J. Chem. Phys.*, 1951, **19**, 649). The main problem is the choice of numerical values for the large number of integrals which appear in the equations. The values given by Craig are derived from the spectrum of ethylene, but this procedure is subject to serious error if the spectrum is incorrectly interpreted and it seems preferable to deduce values for the integrals from their theoretical meanings provided this does not lead to absurdity in the final results.

The usual model for the transition state in aromatic substitution is that due to Wheland (*loc. cit.*). The carbon atom at which substitution occurs is considered to change its hybridisation from trigonal (sp^2) to tetrahedral (sp^3) and thus dissociate itself from the conjugated system. In benzene itself this process will leave a residual conjugated chain of 5 carbon atoms and 4, 5, or 6 electrons according to whether the reactant is electrophilic, homolytic, or nucleophilic.

The transition state for electrophilic substitution in benzene will be a pentadienate cation, which may be considered as a resonance hybrid of singly charged structures such as



and multiply ionised structures such as

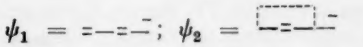


Provided the multiply ionised structures may be neglected the number of integrals required in the calculations is small. These are: Q = coulomb integral, an approximate measure of the electrostatic stability of the structure; α = exchange integral for the interchange of two electrons on adjacent atoms; η = resonance integral for a single-electron jump between adjacent atoms; and ρ = resonance integral for a single-electron jump between two atoms separated by a third atom.

The integral η represents a one-electron jump between two adjacent atoms and might be expected to be about $\frac{1}{2}\alpha$ (it is similar in form to the MO resonance integral β, which has an empirical value of just over $\frac{1}{2}\alpha$). The value of ρ is less easy to estimate. If it is considered to represent a single-electron jump to a non-adjacent atom then the value would be small, but interaction between two singly charged structures in which the charges are situated on alternate atoms can occur through a triply charged structure having like charges on these same atoms and an unlike charge on the intermediate atom. Since in this method singly charged structures alone are included explicitly, this interaction must be allowed for in the value given to ρ. Empirically the value $\frac{1}{4}\alpha$ leads to reasonable conclusions.

The matrix elements in the secular determinant ($H_{rs} = \int\psi_r H\psi_r d\tau$ and $S_{rs} = \int\psi_r\psi_s d\tau$) may be found by the following rules.

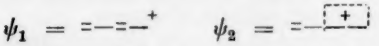
(I) Charges on the same atoms: The simple rules formulated by Pauling (*J. Chem. Phys.*, 1933, **1**, 280) may be used. The matrix term $H_{rs} - ES_{rs} = (\frac{1}{2})^{n-i}(Q - E + b\alpha)$ where n is the number of bonds and i the number of islands in the superposition pattern, and b = number of pairs of neighbour orbits in the same island + the number of unpaired neighbour orbits in the same island separated by an odd number of bonds − 2 (the number of unpaired neighbour orbits in the same island separared by an even number of bonds) − $\frac{1}{2}$ (number of pairs of neighbour orbits in different islands),

e.g., 

then $H_{12} - ES_{12} = \frac{1}{2}(Q - E + 2\alpha)$

(II) Charges on adjacent atoms:

$$H_{rs} = (\tfrac{1}{2})^{n-i} \cdot \eta; \quad S_{rs} = 0$$

e.g., 

then $H_{12} = \eta$

(III) Charges on atoms separated by a third atom :

$$H_{rs} = (\tfrac{1}{2})^{n-1}.\rho; \quad S_{rs} = 0$$

e.g., $\psi_1 =$ =—=—$^{+}$ $\psi_2 =$ =—$^{+}$—=

then $H_{12} = \rho$

Justification for these rules may be found in the theoretical papers referred to above.

Nine singly charged structures (ψ_1 to ψ_9 below) may be drawn for the pentadienate cation. The energy is written below each structure.

=—=—$^{+}$	$^{+}$—=—=	=—[+]
ψ_1 $Q + \frac{3}{2}\alpha$	ψ_2 $Q + \frac{3}{2}\alpha$	ψ_3 $Q + \frac{1}{2}\alpha$
[+]—=—	—=—[+]	[+]—=—
ψ_4 $Q + \frac{1}{2}\alpha$	ψ_5 $Q + 0\alpha$	ψ_6 $Q + 0\alpha$
—=—[+]	[+]—=—	=—$^{+}$—=
ψ_7 $Q + \frac{1}{2}\alpha$	ψ_8 $Q + \frac{1}{2}\alpha$	ψ_9 $Q + 2\alpha$

The wave function may be written as :

$$\Psi = a(\psi_1 + \psi_2) + b(\psi_5 + \psi_6) + c(\psi_3 + \psi_4) + d(\psi_7 + \psi_8) + e\psi_9$$

The four "*meta*" structures ψ_3, ψ_4, ψ_7, and ψ_8 have the same energy, so it is probably reasonable to equate coefficients c and d. The secular determinant then becomes

$$\begin{vmatrix} x + \frac{3}{2} & \frac{1}{2}(x+3) & \frac{3}{4} & \frac{1}{4} \\ \frac{1}{2}(x+3) & x & \frac{3}{4} & \frac{1}{4} \\ \frac{3}{4} & \frac{3}{4} & 3x + \frac{29}{8} & \frac{3}{4} \\ \frac{1}{2} & \frac{1}{2} & \frac{3}{2} & x + 2 \end{vmatrix} = 0$$

where $x = (Q - E)/\alpha$.

This equation may be solved to give an energy $E = Q + 2{\cdot}631\alpha$ and a positive charge distribution

0·114	0·090	0·592	0·090	0·114
$C_{(1)}$	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$

This distribution differs markedly from the normally accepted charge distribution as predicted by MO theory, *viz.* :

0·333	0	0·333	0	0·333

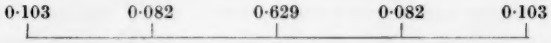
Of the two main reasons, the more important is the greater stability of structure 9 compared with structures 1 and 2, which results in an appreciable localisation of charge on the central atom. In this treatment, as is usual in VB theory, the interaction between the electrons in the C–H bonds and the π-electrons is neglected. When, as with homopolar molecules such as benzene, all the structures included have the same electron distribution this neglect will not affect the result, but when the electron distributions in the structures are different, as in the present case, such neglect will affect the calculated charge distribution. If these interactions were included in the calculation, the stabilities of structures 1 and 2 (*i.e.*, structures with a terminal charge) would be closer to that of structure 9 and the difference in charge would partly, though not entirely, disappear.

The second reason is the neglect of multiply charged structures. The importance of "*meta*-bonded" structures such as ψ_3 is largely due to their enabling the more stable

" Kekulé " structures such as ψ_1 and ψ_9 to interact. This interaction can also occur through multiply charged structures such as :

and although this interaction has been indirectly included in the energy E by the value given to ρ, explicit inclusion of these structures in the wave function would lead to a greater localisation of charge on carbon atoms 1, 3, and 5 as given by the MO theory. However, for such inclusion many new integrals of uncertain value would be required and the significance of the results would be doubtful.

The calculation may be considerably simplified if the " long-bonded " structures ψ_5, ψ_6, ψ_7, and ψ_8 are neglected. This approximation leads to an energy $E = Q + 2{\cdot}565\alpha$ and a charge distribution :



In view of the uncertainty in the values given to the various integrals, this approximation is sufficiently close for qualitative discussion.

To investigate the effect of inductive substituents (or heteroatoms) on the electrophilic substitution of benzene, it may be assumed that the energy of the benzene molecule itself is unaltered by the substituent, but that in the transition state the substituent will affect the coulomb integral for the ionic resonance form in which the positive charge is situated on the carbon atom to which the substituent is attached. The energy of the transition state is then calculated by replacement of the coulomb integral Q for this particular structure in the secular determinant by $Q + y\alpha$. For an electron-attracting $(+I)$ substituent, y will be negative, and for an electron-releasing $(-I)$ substituent y will be positive. The energy E may then be calculated for varying values of y for each of the three different positions in the ion.

For complete accuracy the calculation must be done in full for each value of y required and for each position, but the results may be obtained approximately by use of the theorem (proved in the Appendix) that the change of energy $\delta E = q_r\,\delta Q_r$, where q_r is the charge on atom r in the unsubstituted ion and δQ_r is the change in the coulomb integral (*i.e.*, $y\alpha$). The annexed Table gives the results for a substituent on $C_{(3)}$ in the ion (*i.e.*, *para*-substitution) calculated by the two methods for varying values of y :

y	$-\frac{1}{2}$	$-\frac{1}{4}$	$-\frac{1}{10}$	$\frac{1}{10}$	$\frac{1}{4}$	$\frac{1}{2}$
$\delta E(\alpha)$ (acc.)	−0·27	−0·121	−0·061	0·065	0·132	0·35
$\delta E(\alpha)$ (app.)	−0·31	−0·126	−0·063	0·063	0·126	0·31

The agreement is fair, even for quite large values of y.

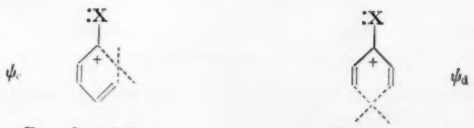
These numerical results lead to the conclusion that, for electrophilic substitution in benzene derivatives, an electron-releasing inductive substituent would activate all three positions and give an order of reactivity *para* > *ortho* > *meta*. The $\frac{1}{2}o : p$ ratio should always be less than 1 and should decrease as the $-I$ effect increases. Electron-attracting substituents should deactivate all three positions and give an order of reactivity *meta* > *ortho* > *para*. The $\frac{1}{2}o : p$ ratio should always be greater than 1 and should increase as the $+I$ effect increases.

$(+I + E)$-Substituents such as the nitro- or cyano-group may be treated similarly. The electromeric effect of these substituents cannot operate to deactivate the reaction, so that the deactivation found with all such substituents must be largely due to their inductive effects together with some deactivation due to the loss of mesomeric conjugation energy, which will tend to strengthen and parallel the inductive effect as it will also be roughly proportional to the positive charge at the position of the substituent in the transition state. It would be predicted that all three positions would be deactivated and the order of reactivity would be *meta* > *ortho* > *para*, the ratios *meta* : *ortho* and *ortho* : *para* increasing with increasing electronegativity of the substituent.

Substituents possessing an activating electromeric effect $(-E)$ can no longer be treated

as simple inductive substituents since the resonance hybrid in the transition state will include triply bonded structures such as :

for *ortho*- and *para*-substitution. These structures are of approximately equal energy so that *ortho*- and *para*-substitution would be equally favoured if these structures were predominant in the transition state. The other main contributing structures for *ortho*- and *para*-substitution are :



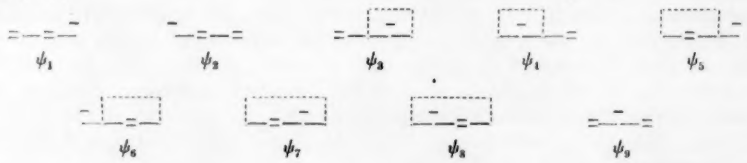
$E = Q + 1{\cdot}5\alpha$ $E = Q + 2{\cdot}0\alpha$

If these structures were predominant, then *para*-substitution would occur to a much greater extent than *ortho*-substitution. Structures ψ_c and ψ_d would be favoured relative to ψ_a and ψ_b by high electronegativity of the substituent X and by a low C–X exchange integral. For any $-E$ substituent it may be predicted that the $\frac{1}{2}o : p$ ratio would always be less than 1 and would decrease with increasing electronegativity of X and to a lesser extent with decreasing C–X exchange integral.

These predictions are generally in agreement with those derived by Dewar (*loc. cit.*) using MO theory and may be exemplified by the experimental evidence quoted there.

Diphenyl may be regarded as benzene with a $-E$ phenyl substituent, so that electrophilic substitution of diphenyl should give predominantly *para*- but together with considerable *ortho*, since the electronegativity of the phenyl group is low. According to MO theory in which electron correlation is ignored both electrophilic and homolytic substitution of diphenyl should occur preferentially at the same position, namely, the *ortho*-position. Experimentally it has been found that nitration (Bell, Kenyon, and Robinson, *J.*, 1926, 1242) gives much more *para*-substitution than phenylation (Cadogan, Hey, and Williams, *J.*, 1954, 794).

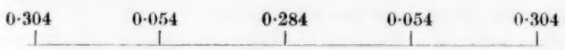
Nucleophilic substitution in benzene derivatives may be treated similarly to electrophilic substitution. The transition state for nucleophilic substitution in benzene itself will be a pentadienate anion which may be regarded as a resonance hybrid of the annexed nine structures.



It was shown that, for the corresponding cation, the structures ψ_5 to ψ_8 could be neglected without seriously affecting the result. If this approximation is made for the anion, the wave function becomes :

$$\Psi = a(\psi_1 + \psi_2) + b(\psi_3 + \psi_4) + c\psi_9$$

The secular determinant may be solved to give an energy $E = Q + 0{\cdot}953\alpha$, and a charge distribution :

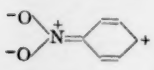
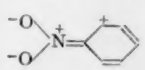


From this distribution it can be predicted that both $+I$ and $(+I + E)$ substituents such as a heteroatom (as in pyridine) or a nitro-group would activate nucleophilic substitution at all three positions and give an order of reactivity *ortho* $\geqslant$ *para* $>$ *meta*. The experimental evidence on this point is not decisive although *ortho*- and *para*-positions in molecules containing such substituents are invariably more active than the *meta*.

The chlorine atom in both *o*- and *p*-chloronitrobenzene is much more labile than in the *meta*-isomer or in chlorobenzene itself, but the relative reactivities of the *ortho*- and the *para*-isomer depend markedly on the reagent. For replacement by piperidine the chlorine atom is much more reactive in the *ortho*-position (Chapman, Parker, and Soanes, *Chem. and Ind.*, 1951, 148), whereas replacement by a methoxide ion occurs more readily in the *para*-position (Miller, *J.*, 1952, 3550). Nevertheless, although the actual rates of replacement depend on the reagent, the relative energies of activation are largely independent of the reagent and are approximately equal for *ortho*- and *para*-substitution, usually with slight favouring of the former. This agrees with the theoretical prediction.

A similar situation arises in nucleophilic substitution in pyridine and its derivatives. No accurate data are available on the activation energies for the replacement of halogen in the halogenopyridines themselves, but by measuring activation energies for the replacement of chlorine by piperidine in 2- and 4-chloroquinoline, Brower, Samuels, Way, and Amstutz (*J. Org. Chem.*, 1953, **18**, 1648) found that the 2-position is more reactive than the 4- and that both are more reactive than the 3-position in quinoline or the 1- and the 2-position in naphthalene.

To explain the high *ortho* : *para* ratio found in electrophilic substitution of nitrobenzene (see De La Mare, *J.*, 1949, 2871) it is usually assumed that in the unperturbed nitrobenzene molecule the "*para*" resonance structure (I) makes a more important contribution to the

(I)   (II)

molecule than the "*ortho*" structure (II), thus placing a larger positive charge on the *para*-position than on the *ortho*-position and deactivating the former more than the latter to electrophilic substitution. If this assumption were true, then in nucleophilic substitution the *para*- would be more reactive than the *ortho*-position, which is contrary to experiment. The assumption has no sound theoretical basis and it seems more probable that the unexpected behaviour of nitrobenzene and similar compounds in electrophilic substitution is due to the importance of electron correlation in determining the energy of the transition state or to the high transmission of inductive effects as discussed by Dewar (*loc. cit.*).

It has already been emphasised that little significance can be placed on the numerical results obtained in this paper because of the uncertainty in the integrals used and the limited number of ionic structures included, but the qualitative results suggest that electron correlation is of some importance in heterolytic substitution reactions. For homolytic substitution the agreement between the VB and MO theories is close, and accurate MO calculations for these reactions will probably give as much agreement with experiment as is possible by the use of molecular wave functions consisting solely of combinations of atomic orbitals.

Appendix

The wave function for any molecule may be written :

$$\Psi = c_1\psi_1 + c_2\psi_2 + c_3\psi_3 + \ldots\ldots$$

This may be substituted in the Schrödinger equation to give :

$$\Psi(H - E)\Psi = (c_1\psi_1 + c_2\psi_2 + \ldots)(H - E)(c_1\psi_1 + c_2\psi_2 + \ldots\ldots) = 0$$

Whence $$c_1^2(H_{11} - ES_{11}) + c_2^2(H_{22} - ES_{22}) + \ldots\ldots + 2c_1c_2(H_{12} - ES_{12}) + \ldots\ldots = 0$$

Now $$S_{11} = S_{22} = S_{rr} = 1 \quad \text{and} \quad S_{rs}\ (r \neq s) = 0$$

therefore $$E(c_1^2 + c_2^2 + \ldots.) = c_1^2H_{11} + c_2^2H_{22} + \ldots\ldots + 2c_1c_2H_{12} + 2c_1c_3H_{13} + \ldots \quad . \quad . \quad . \quad . \quad (1)$$

Since the wave function is normalised,

$$c_1^2 + c_2^2 + c_3^2 + \ldots\ldots = 1$$

and, if there is only one structure with the charge on any particular atom (or if all the structures with the charge on the same atom may be grouped with one coefficient), then $c_r^2 = q_r$, where q_r is the charge on atom r.

Equation (1) may now be written:

$$E = q_1H_{11} + q_2H_{22} + \ldots + 2c_1c_2H_{12} + 2c_1c_3H_{13} + \ldots\ldots$$

In an ion such as the pentadienate cation or anion, H_{rr} is of the form $Q_r + x_r\alpha$ and H_{rs} is of the form $z_{rs}\alpha$; thus

$$E = q_1(Q_1 + x_1\alpha) + q_2(Q_2 + x_2\alpha) + \ldots\ldots + 2c_1c_2z_{12}\alpha + 2c_1c_3z_{13}\alpha + \ldots\ldots$$

Therefore $dE/dQ_1 = q_1$, and hence $\delta E = q_1\delta Q_1$. This relation is true provided that c_1 is independent of Q_1. When δQ_1 is small this will be nearly true, but when δQ_1 is large the change in c_1 with Q_1 will be appreciable. Thus, if δQ_1 is positive, c_1 will increase and δE will be greater than $q_1\delta Q_1$; if δQ_1 is negative, δE will be less than $q_1\,\delta Q_1$.

The author expresses his gratitude to Professor D. H. Hey and Professor H. C. Longuet-Higgins for reading the manuscript and for helpful criticism, and to the Department of Scientific and Industrial Research for the award of a maintenance grant.

UNIVERSITY OF LONDON, KING'S COLLEGE,
STRAND, LONDON, W.C.2.

[*Received, May 17th,* 1954.]

Hydrogen Transfer. Part I. Introductory Survey.

By E. A. BRAUDE and R. P. LINSTEAD.

[Reprint Order No. 5152.]

Reactions involving the transfer of hydrogen in organic systems are classified. The interrelations between such reactions are briefly discussed, and the general background and scope of the work to be described in subsequent parts of this series are indicated.*

REACTIONS in which covalently bonded hydrogen changes its site of attachment, either inter- or intra-molecularly,† are formally amongst the simplest of organic chemical processes. At the same time, they are amongst the most important from both the synthetical and the biochemical point of view. Although many such reactions have been extensively investigated, hydrogen transfer presents many unexplored features of practical as well as theoretical interest. Comparatively little has been done, for example, towards bringing

* For a preliminary summary, see Linstead, Braude, Mitchell, Wooldridge, and Jackman, *Nature*, 1952, **169**, 100.

† Such reactions may be designated by the general term "hydrogen transfer."

the different types of hydrogen transfer into relation with one another and towards establishing a generalised system of hydrogen-donors and hydrogen-acceptors. The existence of a scale of covalent hydrogenation levels, related in certain respects to the scales of ionic hydrogenation levels, *i.e.*, oxidation–reduction potentials in double proton transfer and acid–base strengths in single proton transfer, is implicit in the vast amount of available factual material, but little systematic work has been done on this aspect.

With these and connected objects in view, a broad study of hydrogen-transfer reactions is being undertaken in these laboratories. The purpose of the present introductory paper is to establish briefly the general background, to classify the principal types of hydrogen transfer, and to indicate the plan of our investigations.

Hydrogen transfer, in the sense in which the term is used here, can be classified as follows: (A) hydrogen migration (transfer within one molecule, though not necessarily intramolecular); (B) hydrogen disproportionation (transfer between identical donors and acceptors); (C) transfer-hydrogenation (transfer between unlike donors and acceptors). Each type of reaction could conceivably be brought about by (i) thermal, (ii) homogeneous catalytic, (iii) heterogeneous catalytic, and (iv) photochemical means. Examples of many of the possible categories are known but the state of knowledge over the whole field varies greatly and there are a number of significant gaps, consideration of which suggests several promising new lines of enquiry. As the following summary will show, catalysed hydrogen transfer in homogeneous systems has been very much more fully studied than either thermal, heterogeneously catalysed, or photochemical transfer, and our present investigations are mainly concerned with the last three categories.

Of the three types of thermal hydrogen transfer, migration is normally limited to high temperature ranges since the energy of activation will usually be of the same order as the dissociation energy of a least one of the X–H bonds concerned. A similar limitation exists in thermal disproportionation since the absence of any overall change in bond types in such reactions normally precludes any large free-energy change and any appreciable stabilisation of a bimolecular transition state. Thus *cyclo*hexene is reported not to disproportionate at temperatures as high as 600° in the absence of catalysts (Zelinski, *Ber.*, 1925, **58**, 185) whereas disproportionation is quite rapid even at room temperature in the presence of suitable catalysts (cf. below and Part VI). A few cases of apparently thermal disproportionation of hydroaromatic compounds near 200° have been observed (cf. Cook, Johnston, and Loudon, *J.*, 1950, 537) but it seems probable that even these are in reality heterogeneously catalysed reactions. By contrast, thermal transfer can be envisaged between unlike donors and acceptors such that *both* products are stabilised with respect to the reagents and that the stabilisation becomes effective in the transition state. An excellent example is the reaction between a hydroaromatic or hydroheterocyclic compound and a quinone to give the dehydro-compound and the quinol. This has been employed quite frequently for dehydrogenation at elevated temperatures (Clar and John, *Ber.*, 1930, **63**, 2967; Criegee, *Ber.*, 1936, **69**, 2578; Prokopetz and Pavlenko, *J. Gen. Chem. U.S.S.R.*, 1939, **9**, 1468; Arnold *et al.*, *J. Amer. Chem. Soc.*, 1939, **61**, 1407; 1940, **62**, 983; Campbell *et al.*, *J.*, 1945, 530; 1949, 1555; 1951, 2511; Crawford and Nelson, *J. Amer. Chem. Soc.*, 1946, **68**, 134; Braude, Jones, Sondheimer, and Toogood, *J.*, 1949, 607; Barnes, Pausacker, and Schubert, *ibid.*, p. 1381; Tucker, *ibid.*, p. 2182; Buu-Hoï *et al.*, *J. Org. Chem.*, 1949, **14**, 492, 802; Horner and Merz, *Annalen*, 1950, **570**, 89; Buchta and Kallert, *Annalen*, 1951, **573**, 220; Dost and van Nes, *Rec. Trav. chim.*, 1951, **70**, 403; Holzer, Ziegler, Zinke, Wiesenberger, and Sobotka, *Monatsh.*, 1953, **83**, 180) but has otherwise been little investigated. We have found that such transfers take place under quite moderate conditions and lend themselves to quantitative study; a survey of the reactions of a wide range of quinones with different types of hydrocarbon donors is described in Parts II, III, and IV and further kinetic as well as thermochemical data will be reported later. A second, related example of thermal hydrogen transfer involves nitro-compounds as acceptor and has been observed with Diels–Alder adducts (Clar, *Ber.*, 1936, **69**, 1686; Bergmann *et al.*, *J. Amer. Chem. Soc.*, 1938, **60**, 1331; 1942, **64**, 176; *J. Org. Chem.*, 1942, **7**, 303; Swain and Todd, *J.*, 1942, 626; Braude and Fawcett, *J.*, 1951, 3117) and with hydroheterocyclic compounds (Ziegler and Zeiser, *Annalen*, 1931, **485**, 174) as donors. Whereas we believe

both these examples to involve heterolytic fission of the X–H bonds, contrary to current views (*e.g.*, Waters, "The Chemistry of Free Radicals," Oxford Univ. Press, 1948, p. 257; Dost and Van Nes, *loc. cit.*), thermal transfers involving homolytic fission are well known. Most of these concern unstable free radicals as acceptors, but such reactions can also be realised with "stable" free radicals, and thermal hydrogen transfer between hydroaromatic compounds and one such radical, diphenylpicrylhydrazyl, is described in Part V.

Hydrogen transfer under conditions of homogeneous catalysis is well known and the mechanisms by which various catalysts facilitate the fission of X–H bonds in solution are fairly well understood. Migration is represented by acid- and base-catalysed prototropy (cf. Baker, "Tautomerism," Routledge, London, 1934; "Hyperconjugation," Oxford Univ. Press, 1952; and references there cited). The first case of acid-catalysed hydrogen disproportionation appears to have been noted by Knoevenagel and Fuchs (*Ber.*, 1902, **35**, 1788) in the case of diethyl dihydrolutidinedicarboxylate, while base-catalysed disproportionation occurs in the Cannizzaro reaction (cf. Alexander, *J. Amer. Chem. Soc.*, 1947, **69**, 289; 1948, **70**, 2592; Burr, *ibid.*, 1951, **73**, 5170; Pfeil, *Chem. Ber.*, 1951, **84**, 229) and has also been observed in dihydroquinoline and dihydro*iso*quinoline derivatives (Huntress and Shaw, *J. Org. Chem.*, 1948, **13**, 679; Brodrick and Short, *J.*, 1949, 2587; Johnson and Buell, *J. Amer. Chem. Soc.*, 1952, **74**, 4513). Homogeneously catalysed transfer hydrogenation is represented by the Meerwein–Ponndorf and Oppenauer interconversions of alcohols and aldehydes and ketones in the presence of metal alkoxides (cf. Bersin in "Newer Methods of Preparative Organic Chemistry," Interscience Publ. Corp., New York, 1948; Djerassi in "Organic Reactions," Vol. VI, New York, 1951; Jackman and Macbeth, *J.*, 1952, 3252; Doering and Ashner, *J. Amer. Chem. Soc.*, 1953, **75**, 393) and by the acid-catalysed reduction of olefins by aromatic hydrocarbon donors (Ipatieff, Pines, *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 2123, 3859; 1949, **71**, 3534; 1950, **72**, 1563, 5521). This part of the subject is strikingly more advanced than the remainder and requires no further comment here.

Earlier work on hydrogen transfer under conditions of heterogeneous catalysis has been concerned mostly with reactions at gas–solid interphases, whereas in the present context our interest lies primarily in surface catalysis in liquid systems and it is to such systems that the following remarks mainly refer. Numerous cases of hydrogen migration catalysed by hydrogenation catalysts have been described, particularly for olefinic acids (cf. Moore, *J. Soc. Chem. Ind.*, 1919, **38**, 320; Hilditch and Vidaharti, *Proc. Roy. Soc.*, 1929, *A*, **122**, 552), steroids (cf. Reindel, Walter, and Rauch, *Annalen*, 1927, **452**, 34; Windaus *et al.*, *ibid.*, 1934, **508**, 105; 1938, **534**, 22; **536**, 204; Wieland *et al.*, *ibid.*, 1941, **543**, 34; 1943, **554**, 1; Eck and Hollingsworth, *J. Amer. Chem. Soc.*, 1941, **63**, 2986; Staveley and Bollenback, *ibid.*, 1943, **65**, 1285, 1290, 1600; Henbest, Jones, and their co-workers, *J.*, 1952, 4883; Budziarek, Johnson, and Spring, *J.*, 1953, 534), and terpenes (cf. Wallach, *Annalen*, 1911, **381**, 64; 1914, **403**, 87; 1918, **414**, 349; Richter and Wolff, *Ber.*, 1926, **59**, 1733, Treibs and Schmidt, *Ber.*, 1927, **60**, 2335; Linstead, Michaelis, and Thomas, *J.*, 1940, 1139), as well as a variety of other systems (cf. Levina *et al.*, *J. Gen. Chem. U.S.S.R.*, 1934, **4**, 1250; 1936, **6**, 1092; 1937, **7**, 747; 1938, **8**, 1776; 1939, **9**, 2287; Delépine and Horeau, *Compt. rend.*, 1938, **206**, 27; Badoche, *ibid.*, 1942, **215**, 142; Wiemann and Laude, *ibid.*, 1948, **226**, 345; Small, Turnbull, and Fitch, *J. Org. Chem.*, 1938, **3**, 204; Horning, *ibid.*, 1945, **10**, 263; Weiss and Weiner, *ibid.*, 1949, **14**, 194; Grob and Hofer, *Helv. Chim. Acta*, 1952, **35**, 2095; Leonard and Berry, *J. Amer. Chem. Soc.*, 1953, **75**, 4989). We have found that such migrations can be effected in many systems which also undergo base-catalysed prototropy, but that the two types of migration exhibit quite different structural specificities, as would be expected. Hydroaromatic derivatives are amongst those particularly prone to metal-catalysed hydrogen migration, and such systems also undergo disproportionation on transition metals, often with remarkable ease, as has long been known (cf. Knoevenagel and Bergdolt, *Ber.*, 1903, **36**, 2857; Wieland, *Ber.*, 1912, **45**, 484; Boeseken and Groot, *Rec. Trav. chim.*, 1918, **37**, 255; Zelinski *et al.*, *Ber.*, 1911, **44**, 2305; 1923, **56**, 1249, 1723 *et seq.*; Levina *et al.*, *J. Gen. Chem. U.S.S.R.*, 1936, **6**, 764 *et seq.*; Linstead *et al.*, *J.*, 1937, 1146; 1940, 1134; Serini and Logemann, *Ber.*, 1938, **71**, 186). The ready occurrence of migration and disproportionation in suitable structures suggests that metal-

catalysed transfer-hydrogenation could similarly be effected, provided certain conditions such as co-adsorption of donor and acceptor on the catalyst are fulfilled. Somewhat surprisingly, only a few incidental observations of metal-catalysed transfer-hydrogenation are to be found in the literature, but a systematic study has now shown that such processes can be realised for a wide range of hydrogen-acceptors. The transfer-hydrogenation of ethylenic compounds, nitro-compounds, and certain other types of acceptors, with *cyclo*-hexene and other hydroaromatic donors, is described in Parts VI, VII, and VIII. Kinetic and thermochemical studies on metal-catalysed disproportionation and transfer will be reported subsequently.

We turn lastly to photochemical hydrogen transfer. The electronic spectra associated with X–H bonds lie in the far ultra-violet (cf. Price, *Ann. Reports.*, 1939, **36**, 47; Platt and Klevens, *Rev. Mod. Physics*, 1944, **16**, 182), and photochemical hydrogen transfer brought about by near ultra-violet or visible light usually depends on light absorption in the relevant region by the acceptor. Very few cases of photochemical hydrogen migration or disproportionation are known, but an instructive example of migration occurs in the rearrangement of 1 : 4 : 9 : 10-tetrahydronaphtha-5 : 8-quinones to 1 : 4-dihydronaphtha-5 : 8-quinols (Braude, Jones, and Stern, *J.*, 1947, 1087); here the energy intake (~80 kcal./mole) is through the 3650 Å band of the diacetylethylene system and this reaction is closely analogous to the previously mentioned thermal transfer-dehydrogenation of hydroaromatic compounds by quinones. Photochemical hydrogen transfer between alcohols and quinones, and many similar donor–acceptor combinations, was extensively studied by Ciamician and Silber (*Ber.*, 1901, **34**, 1531 *et seq.*). These transformations are the photochemical analogues to the Meerwein–Ponndorf and Oppenauer reactions (see above), but have found little synthetical use except in the preparation of pinacols (cf. Cohen, *Rec. Trav. chim.*, 1920, **39**, 242; Bachmann, *Org. Synth.*, 1934, **14**, 8; Weizmann, E. Bergmann, and Hirshberg, *J. Amer. Chem. Soc.*, 1938, **60**, 1530; F. Bergmann and Hirshberg, *ibid.*, 1943, **65**, 1429; Moustafa, *Nature*, 1948, **162**, 856). The original investigators reported hardly any details and we are now studying such reactions under controlled conditions. The energy change accompanying the reaction between benzoquinone and methanol to give quinol and formaldehyde can be estimated from bond and resonance energies to be quite small (ΔH *ca.* −5 kcal.), but the corresponding reaction with water to give molecular oxygen is calculated to be endothermic by *ca.* 55 kcal. This increment could theoretically still be supplied through direct light absorption by the quinone, but such reactions, which are closely related to the least well understood step in natural photosynthesis, have so far only been realised in the presence of intact plant cells or chloroplasts (cf. Warburg and Lüttgens, *Naturwiss.*, 1944, **32**, 161; Aronoff, *Plant Physiology*, 1946, **21**, 393; Arnon and Whatley, *Arch. Biochem.*, 1949, **23**, 141; Clendenning *et al.*, *ibid.*, 1950, **29**, 387; *Canad. J. Res.*, 1950, **28**, *C*, 78, 102, 114; Punnett and Fabiyi, *Nature*, 1953, **172**, 947). The systematic investigation of model systems may contribute to the elucidation of this important problem.

Department of Organic Chemistry,
Imperial College of Science and Technology,
South Kensington, London, S.W.7.

[*Received, February 24th*, 1954.]

Hydrogen Transfer. Part II. The Dehydrogenation of* 1 : 4-*Dihydronaphthalene by Quinones. Kinetics and Mechanism.*

By E. A. Braude, L. M. Jackman, and R. P. Linstead.

[Reprint Order No. 5153.]

The dehydrogenation of 1 : 4-dihydronaphthalene by quinones has been studied kinetically in phenetole and other solvents in the range 50—160°. The principal findings are :

(i) The reactions are essentially bimolecular, though deviations from second-order kinetics are frequently observed owing to a variety of causes, which have been analysed.

(ii) The reactions are faster in polar than in non-polar solvents. Radical-producing agents, such as light or benzoyl peroxide, are without influence and no coupling products derived from the hydrocarbon are obtained.

(iii) The reactivity of quinones is enhanced by electron-attracting, and reduced by electron-donating substituents, and the rate constants as well as the energies of activation can be correlated with the reduction potentials of the quinones. *o*-Quinones are more reactive relatively to *p*-quinones than expected from their potentials.

(iv) With quinones of low potential, the reactions exhibit marked product catalysis which is due to the quinol formed. Similar catalytic effects are observed with other weak proton donors which form molecular complexes with quinones (*e.g.*, *p*-nitrophenol) and with very strong proton donors (*e.g.*, perchloric acid).

These observations are rationalised by a two-step heterolytic mechanism involving a rate-determining transfer of a hydrogen atom with its pair of bonding electrons from the hydrocarbon to the quinone, followed by rapid proton transfer between the resulting conjugate acid of the aromatic hydrocarbon and the quinol anion :

$$RH_2 + Q \xrightarrow[\text{Slow}]{} R{\cdot}H^+ + QH^- \xrightarrow[\text{Fast}]{} R + QH_2$$

Catalysis by proton donor is ascribed to the formation of the conjugate acid of the quinone, *i.e.*, the quinol cation QH^+, which has an even higher affinity for anionoid hydrogen than the quinone :

$$Q + HX \underset{\text{Fast}}{\rightleftharpoons} QH^+{\cdot}X^-,\ RH_2 + QH^+ \xrightarrow[\text{Slow}]{} R{\cdot}H^+ + QH_2,\ RH^+ + X^- \xrightarrow[\text{Fast}]{} R + HX$$

This paper is the first of a number which will deal with kinetic investigations of the dehydrogenation of hydroaromatic compounds by quinones. Such reactions are not only of practical interest, but also provide particularly attractive examples of thermal hydrogen transfer for quantitative study. Both reactants are readily capable of wide structural variation, a considerable amount of information concerning their thermodynamic properties is available, and convenient as well as accurate analytical methods can be devised. The majority of preparative applications of dehydrogenations with quinones refer to tetrahydro-compounds (for references, see Part I *), but, for the sake of simple stoicheiometry and ease of reaction, a dihydro-derivative was preferable for an initial study. We chose 1 : 4-dihydronaphthalene as a suitable donor and have examined the kinetics of its reaction with benzoquinone and a representative series of other quinones to give naphthalene and the quinols.

Transfer occurs at convenient speeds, and in most cases quantitatively, in the temperature range 50—160° in suitable solvents; in a preparative experiment, 1 : 4-dihydronaphthalene was heated with benzoquinone in diethylene glycol diethyl ether for 72 hr. at 131° and naphthalene was isolated in 90% yield. For the majority of kinetic experiments, phenetole, which has satisfactory solvent power for a wide range of quinones and quinols

* Part I, preceding paper.

and is stable for prolonged periods at elevated temperatures, was used. Two methods were employed for determining reaction rates. In the first, the disappearance of quinone was followed by reduction of aliquot portions with titanous chloride. The direct estimation of quinones in this manner was first described by Knecht and Hibbert (" New Reduction Methods in Volumetric Analysis," Longmans, Green and Co., London, 1910, p. 89) but a more accurate procedure consists in using excess of reducing agent and back-titration with ferric ammonium sulphate against an indicator of lower potential than the quinone. In order to obtain sharp end-points, the potential difference between quinone and indicator should be at least 0·2 v; methylene-blue was found suitable for quinones with $E^\circ > 0{\cdot}55$ v; and rosinduline ($E^\circ = -0{\cdot}28$ v) for quinones with $E^\circ < 0{\cdot}55$ v. In the second method, the appearance of quinol was followed by oxidation with ceric ammonium sulphate, with diphenylamine ($E^\circ = +0{\cdot}85$ v) as indicator. This method is not applicable to 1 : 2-quinols, since 1 : 2-quinones undergo rapid further oxidation; 1 : 4-quinones are also attacked by ceric ions but usually sufficiently slowly to allow a good end-point to be obtained. In a number of cases it was possible to combine the two methods, and thus obtain a check on the stoicheiometry of the reaction, by using ceric instead of ferric ammonium sulphate in the back-titration of titanous chloride against methylene-blue, and then continuing the titration after addition of diphenylamine until the second end-point was reached.

The reactions between dihydronaphthalene and 1 : 4-benzoquinone, toluquinone, chlorobenzoquinone, and tetrachlorobenzoquinone in phenetole and a number of other solvents were found to obey strictly second-order rate laws (first-order with respect to each reactant), both at equimolar concentrations of hydrocarbon and quinone and when one reactant was present in excess, provided aerial oxygen was excluded more or less rigorously (depending on the oxidation–reduction potential) to prevent re-oxidation of the quinols. The reactions with the other quinones studied also exhibited essentially second-order kinetics, but showed various types of deviations, as follows.

(1) With 2 : 6-dichloro- and trichloro-1 : 4-benzoquinone, a marked decrease in the second-order rate constants was observed as the reaction proceeded. Separate experiments showed that this was not due to the thermal instability of the quinones, quinols or quinhydrones, and that no reaction occurred between the quinols and either dihydronaphthalene or naphthalene under the conditions used. It is therefore probable that side-reactions between these quinones and dihydronaphthalene are responsible for the effect; two possibilities are the formation of (non-oxidisable) quinol diethers,* which has also been observed in other cases (Criegee, *Ber.*, 1936, **69**, 2758; Farmer, *Trans. Faraday Soc.*, 1942, **38**, 341) and the formation of naphthyl-substituted quinones or quinols which would result in more than equimolar consumption of dihydronaphthalene.

(2) The reaction with 1 : 4-naphthaquinone also exhibits a downward drift of the second-order rate constants when the reaction is followed by estimation of the quinol produced. Separate experiments showed that, in this case, the effect is at least partly due to thermal instability of 1 : 4-dihydroxynaphthalene. The fact that the ceric sulphate titre of the latter in phenetole decreases to a constant value corresponding to about 75% of the initial value suggests that reversible isomerisation to 1 : 4-dihydro-1-hydroxy-4-oxonaphthalene (Madinaveitia and Olay, *Anal. Fís. Quím.*, 1933, **32**, 1157 *et seq.*), analogous to the oxanthrol–oxanthrone rearrangement in the anthracene series, might be responsible.

(3) With 2 : 5- and 2 : 6-dimethylbenzoquinone, thymobenzoquinone (2-methyl-5-*iso*propylbenzoquinone), 1 : 2-naphthaquinone, and 9 : 10-phenanthraquinone, all of which have oxidation–reduction potentials less than 0·6 v, the second-order rate constants, though accurately reproducible, increase as the reaction proceeds. The drifts are generally larger the lower the potential of the quinone, but they also decrease with increasing temperature and depend markedly on the solvent and other experimental conditions. Thus, for a 0·1M-solution in phenetole at 100°, the ratio k (after 50% reaction) : k (extrapolated to zero time) was 1·55 for thymoquinone (E° 0·589), 1·80 for 1 : 2-naphthaquinone (E° 0·579), and 2·00 for 9 : 10-phenanthraquinone (E° 0·471), while for thymoquinone at

* Some quinol diethers are readily oxidisable; *e.g.*, 1 : 4-dimethoxybenzene.

155° the ratio was 1·2. The possibility that these effects might be due to the simultaneous occurrence of first-order reactions was eliminated in the following way. If the rate law were $dx/dt = k_2(a - x)^2 + k_1(a - x)$ (where a refers to the initial concentration of both reactants and x is the fraction which has undergone change at time t), then

$$k_2 = (1/\alpha t) \ln [a(a - x - \alpha)/(a + \alpha)(x - a)]$$

where $\alpha = k_1/k_2$. However, when this equation was solved for α from results of runs with thymoquinone at different values of a, a constant value for α was not obtained [See runs (xiv)—(xvi), p. 3561]. The upward drift in the second-order rate constants was eventually found to be due to a catalytic effect of the quinol produced; initial addition of 0·5 mol. of quinol increased the extrapolated rate constant by about 20%, while in the presence of 1·2 mols. of quinol, the rate constants were approximately doubled and little deviation from second-order kinetics was then observed during the first half of the reaction. On the other hand, the initial addition of the other reaction product, naphthalene, is without effect. The occurrence of product-catalysis due to quinol has important mechanistic implications and is further discussed below.

Second-order rate constants (extrapolated, where necessary, to zero time) for the reaction of 1 : 4-dihydronaphthalene and twelve quinones in phenetole are given in Table 1. In the four cases in which strict second-order kinetics were observed, the average deviation was about 1%; the accuracy of extrapolated rate constants is somewhat lower. In each case, the plots of log k_2 against $1/T$ were satisfactorily linear and the Arrhenius energies of activation (E_A), entropies of activation ($\Delta S^\ddagger$), and free energies of activation ($\Delta G^\ddagger$) are given in Table 2, together with the oxidation–reduction potentials ($E°$) of the quinones in ethanol at 25°, determined by Conant and Fieser (*J. Amer. Chem. Soc.*, **1923**, **45**, 2194; 1924, **46**, 1858).

TABLE 1. *Second-order rate constants* (10^4k *in l. mole*$^{-1}$ *sec.*$^{-1}$) *for the reaction between* 1 : 4-*dihydronaphthalene and quinones in phenetole.*

	50°	60°	70°	80°	90°		
Trichloro-1 : 4-benzoquinone	0·274	0·608	1·30	2·80	5·53		
2 : 6-Dichloro-1 : 4-benzoquinone	0·313	0·687	1·47	2·94	5·90		
1 : 2-Naphthaquinone	—	0·547	1·01	2·12	4·21		
	90°	**100°**	**110°**	**119°**	**131°**	**141°**	**155°**
Tetrachloro-1 : 4-benzoquinone	7·85	15·7	28·3	59·4	100	—	—
Chloro-1 : 4-benzoquinone	2·37	4·57	8·48	14·4	28·3	—	—
1 : 4-Benzoquinone	—	1·21	2·62	4·26	7·95	15·1	—
Toluquinone	—	0·399	0·825	1·42	3·27	5·90	—
2 : 6-Dimethyl-1 : 4-benzoquinone	—	0·140	—	—	1·25	—	5·28
2 : 5-Dimethyl-1 : 4-benzoquinone	—	0·0849	—	0·309	0·811	1·48	3·51
2-Methyl-5-*iso*propyl-1 : 4-benzoquinone	—	0·0633	—	0·254	0·610	1·15	2·81
1 : 4-Naphthaquinone	—	0·0157	—	0·0635	0·151	0·320	0·842
9 : 10-Phenanthraquinone	0·380	0·722	1·14	2·24	5·19	—	—

TABLE 2. *Thermodynamic quantities of activation for the reaction between* 1 : 4-*dihydronaphthalene and quinones in phenetole.*

No.	$-\log k_{100°}$	E_A (kcal./mol.)	$\Delta S^\ddagger_{100°}$ (e.u.)	$\Delta G^\ddagger_{25·0°}$ (kcal./mol.)	$E°_{25·0°}$ (v)
1. Tetrachloro-1 : 4-benzoquinone	2·80	18·2	−25·1	25·0	0·703
2. Trichloro-1 : 4-benzoquinone	3·00 *	17·7	−27·3	25·1	0·726
3. 2 : 6-Dichloro-1 : 4-benzoquinone	3·00 *	17·0	−29·0	24·9	0·748
4. Chloro-1 : 4-benzoquinone	3·34	17·7	−28·9	25·6	0·736
5. 1 : 4-Benzoquinone	3·92	18·9	−28·2	26·6	0·711
6. Methyl-1 : 4-benzoquinone	4·40	20·3	−26·8	27·6	0·656
7. 2 :6 -Dimethyl-1 : 4-benzoquinone	4·85	21·1	−26·9	28·3	—
8. 2 : 5-Dimethyl-1 : 4-benzoquinone	5·07	21·8	−26·0	28·8	0·597
9. 2-Methyl-5-*iso*propyl-1 : 4-benzoquinone	5·20	22·0	−25·9	28·9	0·589
10. 1 : 4-Naphthaquinone	5·80	23·0	−26·1	30·0	0·493
11. 1 : 2-Naphthaquinone	3·14 *	16·6	−31·0	25·0	0·579
12. 9 : 10-Phenanthraquinone	4·14	18·5	−30·5	26·7	0·471

* Extrapolated from the k–T data by the method of least squares.

Discussion

Only two previous quantitative investigations of thermal dehydrogenation processes with quinone acceptors are on record. The first was carried out by Dimroth and his pupils (*Angew. Chem.*, 1933, **46**, 571; 1938, **51**, 404) who employed diethyl 1 : 4-dihydrocollidine-2 : 6-dicarboxylate and *o*-tolylphenylsemicarbazide as donors. Only a summary of the results published shortly before Professor Dimroth's death is available, but it was established that the reactions exhibit the expected second-order kinetics and that an approximately linear relation obtains between log k_2 and the redox potentials of the quinones, determined in the same solvent, acetic acid. Since the preliminary report (*Nature*, 1952, **169**, 100) of our work, Dost (*Rec. Trav. chim.*, 1952, **71**, 857) has reported a study of the dehydrogenation of 1 : 2-dihydronaphthalene, acenaphthene, and certain other hydrocarbons by chloranil in chlorobenzene and also compared the reactivity of different quinones. He, too, found the reactions to be of the second order and obtained qualitative evidence for a correlation between dehydrogenating power and redox potential.

The present results confirm the conclusion that transfer reactions of this type are essentially bimolecular, though deviations from second-order kinetics due to catalytic

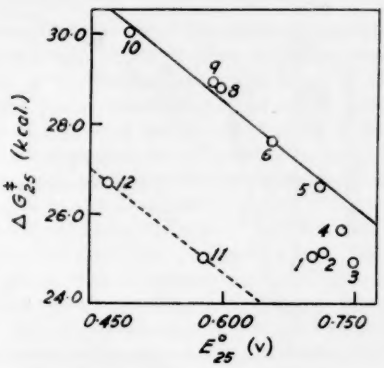


Fig. 1. *Plot of free energies of activation for dehydrogenation of* 1 : 4*-dihydronaphthalene in phenetole against oxidation–reduction potentials of quinones in ethanol. The numbers refer to the quinones listed in Table* 2.

effects of the quinols or side-reactions are frequently observed. The results in Table 2 also show that there is a roughly linear correlation between $\Delta G^{\ddagger}$ and the potentials of 1 : 4-quinones in ethanol solution (Fig. 1), but that the relation breaks down entirely in comparing 1 : 4-quinones with 1 : 2-quinones; the latter are far more reactive although their potentials are smaller. A similar difference, though surprisingly in the opposite direction, was noted by Dimroth (*loc. cit.*) who found that tetrabromo-1 : 2-benzoquinone was less reactive than would be expected from the plot of log k against E° for 1 : 4-quinones.

Since the potentials are a measure of the free-energy gain in converting the quinones into the quinols, some correlation with reactivity is to be expected independently of the reaction mechanism, though the precise relations will depend on the extent to which the additional resonance stabilisation of the quinol is effective in the transition state, as well as on a variety of other factors. A more detailed analysis of the results (Table 2) shows that the rate differences in the transfer reaction are mainly due to differences in the energies of activation E_A, whereas the entropies of activation $\Delta S^{\ddagger}$ exhibit small and irregular fluctuations. In relation to redox potentials, which are effectively a measure of the free-energy changes of the reduction of quinone by molecular hydrogen, the most comparable kinetic parameters are the free energies of activation $\Delta G^{\ddagger}$, and the values for five 1 : 4-quinones may be expressed within experimental error by the relation

$$\Delta G^{\ddagger}_{25^{\circ}} = 38{\cdot}0 - 0{\cdot}0016E^{\circ}_{25^{\circ}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

or, the potentials being converted into free energies,

$$\Delta G^{\ddagger}_{25^{\circ}} = 38{\cdot}0 - 0{\cdot}07\Delta G^{\circ}_{25^{\circ}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where E° (in v) and ΔG° (in kcal.) refer to ethanol solutions (Conant and Fieser, *loc. cit.*). The only 1 : 4-quinones of known potentials which deviate from this relation are trichloro- and tetrachloro-benzoquinone, and it is significant that the potentials of these two quinones *in ethanol* are somewhat abnormal; whereas E° is increased by one and by two chlorine substituents, the third and fourth substituent each cause a decrease. This appears to be due to a specific solvent effect, for in benzene a decrease in E° occurs only with tetrachloro-1 : 4-benzoquinone, while the potentials referred to the gaseous state show a regular increase throughout the series (Conant, *J. Amer. Chem. Soc.*, 1927, **49**, 293; Hunter and Kvalnes, *ibid.*, 1932, **54**, 2869; Kvalnes, *ibid.*, 1934, **56**, 667, 670; Evans and De Heer, *Quart. Reviews*, 1950, **4**, 94). The free energies of the dehydrogenation of 1 : 4-dihydronaphthalene in phenetole exhibit a dependence on chlorine substitution in the quinone which is actually intermediate in type between that of the potentials in benzene and in ethanol (Fig. 2); since the solvating properties of phenetole are likely to be intermediate between those of benzene and ethanol, this suggests that the quinonoid species concerned in chemical and electrochemical hydrogen transfer are indeed closely similar, if not identical. The fact that, for a limited range of quinones, a straight-line relation between the free energies of

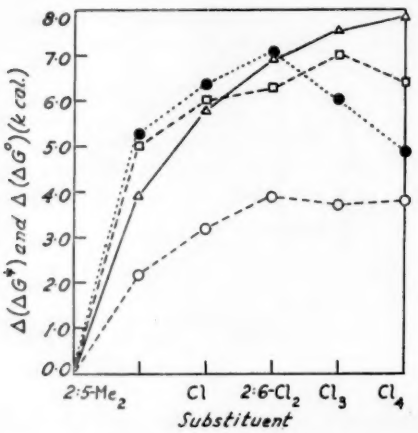


FIG. 2. *Effects of substituents in benzoquinone on the free energy of activation for dehydrogenation of* 1 : 4-*dihydronaphthalene in phenetole* (– – – ○ – – – ○ – – –), *and on the free-energy changes accompanying reversible reduction by hydrogen in ethanol* (· · · ● · · · ● · · ·), *in benzene* (– – – □ – – – □ – – –) *and in the gas phase* (——△——△——) (*calculated from oxidation–reduction potentials*).

the two processes obtains even in two different solvents indicates that, in the absence of several highly polar substituents, the differential effects of solvation are quite small. In this connection, it is of interest that the entropy changes in the electrochemical reduction of benzoquinone and toluquinone (the only two for which data are available) are very similar (*ca.* 30 e.u.; Conant and Fieser, *loc. cit.*) to those observed in the transfer reaction (Table 2).

We now turn to a consideration of the mechanism of the transfer reaction. It was suggested by Waters (*Trans. Faraday Soc.*, 1946, **42**, 184; "The Chemistry of Free Radicals," Oxford Univ. Press, 1946) that such processes are homolytic and involve the abstraction of a hydrogen atom by the quinone to give a semiquinone radical. The experimental basis of this suggestion was that the autoxidation of tetralin is inhibited by quinones and, although this fact can be explained in this manner, other interpretations are possible which do not involve homolytic hydrogen transfer to the quinone. Dost and van Nes (*Rec. Trav. chim.*, 1951, **70**, 403) also considered that dehydrogenation of hydroaromatic compounds by quinones proceeded by a free-radical mechanism, but their general arguments in favour of this view are not very convincing, and attempts to catalyse the reactions by ultraviolet light or by peroxides gave negative results. A similar lack of acceleration due to radical-producing agents has been observed here; thus the rate constant for the dehydrogenation of 1 : 4-dihydronaphthalene by thymoquinone in phenetole at 155° was unchanged within experimental error in the presence of 0·005M-benzoyl peroxide which undergoes rapid homolysis at this temperature (Bartlett and Nozaki, *J. Amer. Chem. Soc.*, 1946, **68**, 1686;

1947, **69**, 2299) or on illumination, and further examples are given in Part IV. As Dost and van Nes have rightly pointed out, such observations do not exclude a homolytic mechanism, though they do make it unlikely that a free-radical chain reaction is involved. Very recently, Moore and Waters (*J.*, 1953, 3405) showed that chloranil reacts under illumination with toluene and xylene to give the quinol and coupling products, and with excess of tetralin to give 1 : 2-dihydronaphthalene. They concluded that all these reactions were photochemical and, therefore, homolytic. However, no control experiments are recorded and although Moore and Waters's interpretation is probably correct for the alkylbenzenes, comparison with results obtained in the absence of illumination (Part IV) indicates that the photochemical effect was negligible for the hydroaromatic donor, tetralin; it is significant that no coupling products of the type expected from homolytic reactions were encountered in this instance. In any case, the existence of a photochemical reaction does not, in itself, prove that the corresponding thermal reaction is homolytic. The only indubitable example of thermal homolytic dehydrogenation by a quinone in solution appears to be the conversion of 3 : 3 : 4 : 4-tetraphenylhexane into diphenylethylene described by Ziegler and Deparade (*Annalen*, 1950, **567**, 123); this belongs to a different category since homolytic dissociation into diphenylpropyl radicals precedes transfer so that the actual donor is itself a free radical.

In agreement with the previous evidence, the kinetic features of the reactions studied here render a free-radical chain mechanism highly unlikely, although they do not as such exclude homolytic as opposed to heterolytic fission of the carbon–hydrogen bond in the donor. In order to obtain further evidence on this point, the influence of solvent was investigated in more detail (Table 3). An increase in rate with increasing polarity of the solvent is observed, which is larger than would be expected for a homolytic process (cf. Waters, *op. cit.*) and corresponds in order of magnitude to that generally encountered in bimolecular heterolytic reactions involving a high degree of charge-dispersal in the transition state (cf. Glasstone, Laidler, and Eyring, "The Theory of Rate Processes," McGraw-Hill, New York, 1941; for a recent example, see Brown and Grayson, *J. Amer. Chem. Soc.*, 1953, **75**, 6285). Attempts to demonstrate a salt effect with thymoquinone and lithium chloride in dimethylformamide or propionic acid were not successful; the quinone, which is reasonably stable in these solvents alone, undergoes rapid changes in the presence of the salt (M) and although the reaction with dihydronaphthalene appeared to be accelerated even more strongly, the results are not considered reliable without more detailed investigation of these systems.

TABLE 3. *Solvent effects in the dehydrogenation of* 1 : 4-*dihydronaphthalene by quinones.* (*Second-order rate constants* $\times 10^4$ *in l. mole*$^{-1}$ *sec.*$^{-1}$).

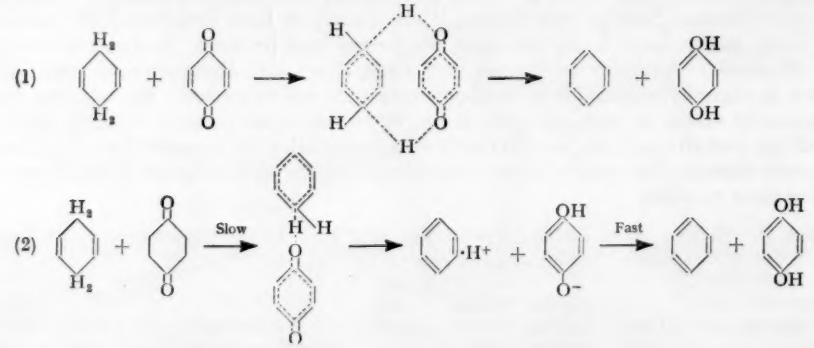
Solvent	Temp.	Thymo-quinone	Benzo-quinone	Chloro-benzo-quinone
Decalin	100°	0·0623	—	—
Diethylene glycol diethyl ether	100	—	1·21	—
Phenetole	100	0·0633	1·21	4·43
o-Dichlorobenzene	100	0·102	1·85	6·55
Dimethylformamide	100	0·288	2·27	8·50

Solvent	Temp.	Thymo-quinone
Phenetole	141°	1·21
Propionic acid	141	3·18
Propionic acid–water (19 : 1, v/v)	141	4·16
Propionic acid–water (9 : 1; v/v)	141	4·88
Phenetole	155°	2·93
o-Dichlorobenzene	155	3·20
Nitrobenzene	155	5·14

The criteria so far applied being inconclusive, the effects of structure on the reactivity of quinones can next be invoked in attempting to classify the reaction. The close parallelism expressed in relations (1) and (2) (p. 3551) between equilibrium in electrochemical reduction and reaction rate in thermal hydrogen transfer indicates that the quinones act as electron-acceptors in both types of processes. That this is indeed the case can be seen, without considering redox potentials, from the fact that the reactivity is increased by electron-attracting substituents (*e.g.*, Cl) and decreased by electron-donating substituents (*e.g.*, Me). From this viewpoint, the correlation with redox potentials is due to the circumstance that electron-attracting substituents decrease, and electron-donating

substituents increase, the stability of the quinone relative to the quinol, because the double-bonded oxygen atoms in the former are electron-demanding (C=C–C=O ⟷ C^+–C–C=O^-) while the single-bonded oxygen atoms in the latter have a mesomeric effect (C=C–$\ddot{O}$H ⟷ C^-–C=O^+H) of the opposite sign. Although the qualitative effects of substituents thus leave no doubt that the quinone acts as an electrophilic reagent, they do not necessarily exclude a homolytic process in which the quinone is an electron-acceptor (cf. Breitenbach and Folly, *Monatsh.*, 1953, **84**, 319; Lopez Aparicio and Waters, *J.*, 1952, 4666; Dunn and Waters, *J.*, 1953, 2993; Dunn, Waters, and Roitt, *J.*, 1954, 584, and earlier papers). The quantitative relations, however, favour a heterolytic process and, summarising, we may say that the absence of side-reactions involving the hydrocarbon, the effects of reaction medium, and the influence of substituents in the quinone all point in the same direction.

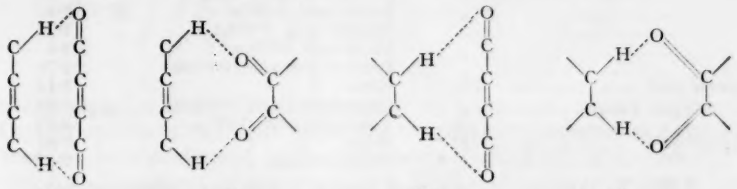
The conclusions so far reached can be accommodated in two types of mechanism. In the first (1), the two hydrogen atoms are transferred more or less simultaneously from the hydrocarbon to the quinone, through a pseudocyclic transition state. In the second (2), one hydrogen atom with its electron pair is transferred through a linear transition state to give the conjugate acid of the dehydrogenation product and the quinol anion, and this is followed by the rapid transfer of the other hydrogen atom in the form of a proton, not necessarily to the same acceptor molecule. The two mechanisms represent the extremes of a range characterised by the varying time-sequence of the two C–H bond fissions; in the one-step mechanism (1), the two events are linked to a high degree, while in the two-step mechanism (2) they are essentially independent. In both mechanisms, a rapid reversible association of the reacting partners might precede the rate-determining step. (For simplicity, the two schemes have been written for 1 : 4-dihydrobenzene and benzoquinone.) In scheme (1) (below) the two rings are supposed to be in different but approximately parallel planes in the transition state.



In the one-step mechanism (1), the quinone is a bifunctional reagent, with one carbonyl group displaying electrophilic, and the other nucleophilic, reactivity. If the time-sequence of hydrogen transfer to both carbonyl groups were completely synchronised, the electronic classification of the reagent would lose its meaning and the influence of substituents would have to be ascribed almost entirely to the change in stabilisation of the quinol which would be partly effective in the transition state. In addition, any differential effect of substituents on the two carbonyl groups, which would facilitate a bipolar condition, might make itself felt, and the somewhat higher reactivity of unsymmetrically as compared with symmetrically substituted methyl- and chloro-quinones (Table 1) might be explained in this way. A diagnostically sharper consequence of the single-step mechanism (1) is that the ease of reaction should be closely dependent on the geometrical relations between the donor and the acceptor; the spatial arrangement of the hydrogen and oxygen atoms must be such as to allow the formation of the pseudocyclic transition state without appreciable strain. It is not immediately obvious in the case of a donor of 1 : 4-dihydrobenzene type whether this condition is better fulfilled by a 1 : 2-quinone or a 1 : 4-quinone (Fig. 3*a* and *b*); but in the case of a donor of 1 : 2-dihydrobenzene type, it is certainly better fulfilled by a

1 : 2-quinone (Fig. 3*c* and *d*). The fact that the ratios of the rate constants for the reactions of 1 : 2- and 1 : 4-naphthaquinone with 1 : 2-dihydronaphthalene and 1 : 4-dihydronaphthalene are similar (Part III) is strong evidence against a single-step mechanism and further evidence is provided by the high reactivity of 1 : 8-diphenoquinones (Braude, Brook, Linstead, and Shannon, unpublished work). On the other hand, on the basis of mechanism (2), the relatively high reactivity of 1 : 2-quinones is understandable since, in contrast to 1 : 4-quinones, both carbonyl groups can participate in the removal of hydride ion in the rate-determining step, and the resulting quinone anion will be stabilised to a greater extent than quinol itself by intramolecular hydrogen bonding. The existence of such additional stabilisation is clearly indicated by the fact that, even in aqueous solution, catechol (pK 9·1) is a stronger acid than either phenol or quinol (pK 9·9) (Abichandani and Jatkar, *J. Indian Inst. Sci.*, 1938, **21**, *A*, 417; Gawron, Duggan, and Grelecki, *Analyt. Chem.*, 1952, **24**, 969).

FIG. 3. *Schematic representation (side views) of transition states for synchronised hydrogen-transfer between* 1 : 4- *and* 1 : 2-*dihydro-donors and* 1 : 4- *and* 1 : 2-*quinones.*



(*a*) (*b*) (*c*) (*d*)

We are thus led, by a process of elimination, to adopt the two-step mechanism (2).* Additional confirmation is provided by the observation (p. 3550) that quinols catalyse transfer to low-potential quinones. Since low-potential quinones are particularly prone to quinhydrone formation (cf. Hunter and Northey, *J. Phys. Chem.*, 1933, **37**, 875), it was suspected that the catalytic effect might be associated with this phenomenon. The catalytic effect does not merely depend on molecular complex-formation by the quinone, however, for, although *p*-nitrophenol and picric acid proved to be strong catalysts, *p*-nitroanisole was ineffective (Table 4); yet all these compounds may be expected to form molecular compounds of the same type with quinones (cf. Wallwork and Harding, *Nature*, 1953, **171**, 40). An attempt to establish whether the quinol dimethyl ether is a catalyst failed because the ether is, somewhat unexpectedly, oxidised by ceric sulphate, but the clear-cut difference between nitrophenol and nitroanisole indicates that the catalytic effect is specific to proton-donors. In phenetole as a solvent, it appears that both complex-forming and acidic properties are needed, for no accelerating influence was shown by acetic or benzoic acid at comparable concentrations. Phenetole, however, is a relatively basic solvent and the absence of general acid catalysis could be due to the fact that the very weakly basic quinone is unable to compete successfully for the proton donor. Some experiments were therefore carried out in propionic acid solution. The considerably increased rate of reaction, compared with that in phenetole, could be a general solvent effect and does not necessarily signify acid catalysis, but a further slight, though significant, acceleration is observed with quite low concentrations of chloroacetic acid in propionic acid, and an enormous acceleration (representing a rate factor of *ca.* 10^3) is produced by perchloric acid, known to be a particularly powerful proton donor under such conditions (cf. Hall, *Chem. Reviews*, 1931, **8**, 191; Kolthoff, *J. Amer. Chem. Soc.*, 1934, **56**, 1007; Mackenzie and Winter, *Trans. Faraday Soc.*, 1948, **44**, 159). Unfortunately, side-reactions occur in this highly acidic solvent and hydrogen transfer could only be followed to about 20% completion. The side-reactions probably include acid-catalysed isomerisation of 1 : 4- to 1 : 2-dihydronaphthalene (which undergoes dehydrogenation much less readily; Part III) as well as addition of propionic acid to the ethylenic double bond (cf. Tilichenko,

* The precise state of the conjugate acid of the aromatic hydrocarbon produced in the rate-determining step has been deliberately left undefined at this stage. Further evidence concerning this detail is presented in Part III.

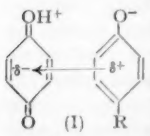
Zhur. Obshchey Khim., 1950, **20**, 2152; Braude and Forbes, *J.*, 1953, 2208; Knight, Coos, and Swern, *J. Amer. Chem. Soc.*, 1953, **75**, 6212) and self-condensation of the quinone (cf. Ioffé and Sukhina, *Zhur. Obshchey Khim.*, 1953, **23**, 1370). As a check, the general acid catalysis of hydrogen transfer was tested with 9 : 10-dihydroanthracene in which prototropic rearrangement is unlikely to occur. The more than two-fold acceleration produced by 0·1M-trichloroacetic acid in propionic acid provides clear evidence of proton catalysis.

TABLE 4. *Effects of various addenda on the rate of dehydrogenation of* 1 : 4*-dihydronaphthalene by thymoquinone* (both reactants 0·1M).

Solvent	Temp.	Addendum	10^4k_2 (l. mole^{-1} sec.$^{-1}$)
Phenetole	155°	None	2·93
,,	,,	Naphthalene, 0·1M	2·88
,,	,,	Thymoquinol, 0·05M	3·43
,,	,,	,, 0·12M	5·50
,,	,,	*p*-Nitrophenol, 0·058M	6·13
,,	,,	*p*-Nitroanisole, 0·058M	2·90
,,	,,	Acetic acid, 0·058M	2·87
,,	,,	Benzoic acid, 0·058M	2·78
,,	,,	Picric acid, 0·058M	3·8
,,	,,	Benzoyl peroxide, 0·045M	2·70
Propionic acid	141	None	3·18
,,	,,	Chloroacetic acid, 0·058M	3·33
,,	23	Perchloric acid, 0·070M	0·92
Propionic acid	141 *	None	0·97
,,	,, *	Trichloroacetic acid, 1M	2·27

* With 9 : 10-dihydroanthracene in place of dihydronaphthalene as donor.

Since addition of a proton to the hydrocarbon could not possibly assist its dehydrogenation, the catalytic effect clearly depends on the partial conversion of the quinone into its conjugate acid. The latter would indeed be expected to be a far more powerful reagent than the quinone itself for dehydrogenation by the two-step mechanism; the presence of a positive charge will greatly increase the electrophilic reactivity of the carbonyl group and the abstraction of a hydride ion from the donor will convert the acceptor directly into the quinol (2*a*). The reactivity of the conjugate acids of the quinones must exceed that of the quinones by many powers of ten, for the extent of conversion when the catalytic effect first becomes noticeable must be extremely small. It is highly probable that in a basic solvent such as phenetole where only proton donors which form molecular complexes with the quinone are effective, the proton transfer is only partial, to give an ion pair in which the charge resonance due to π-bonding (cf. Mulliken, *J. Amer. Chem. Soc.*, 1952, **74**, 811) is reinforced by charge resonance due to proton transfer, as represented in (I). The fact that product-catalysis due to the quinol is observed only with quinones of low potential indicates that electron-donating substituents increase the basicity of the quinone more than they reduce the acidity of the quinol (cf. Hunter and Northey, *J. Phys. Chem.*, 1933, **37**, 875). This picture is also in accord with the fact that product-catalysis decreases with increasing temperature which will reduce the extent of molecular-complex formation (cf. Gibson and Loeffler, *J. Amer. Chem. Soc.*, 1940, **62**, 1324) and with increasing ionising properties of the solvent, which will have the same effect since they favour charge dispersal.*



(I)

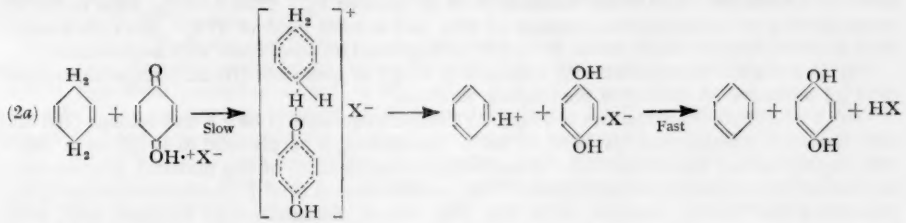
Reactions involving displacement of hydrogen in an anionoid condition (hydride ion),

* It should be mentioned that, in isolation, proton catalysis could conceivably be accounted for by the homolytic variant of mechanism (2*a*), as was first pointed out to us by Professor J. D. Roberts (California). In such a scheme, the conjugate acid of the quinone would be converted into a radical cation in the rate-determining step :

$$RH_2 + QH^+ \longrightarrow RH\cdot + QH_2{}^{\cdot+},\ QH_2{}^{\cdot+} \longrightarrow QH\cdot + H^+,\ RH\cdot + QH\cdot \longrightarrow R + QH_2$$

Evidence has recently been reported for the stabilisation of quinone diradicals in strongly acid media (Hirshon, Gardner, and Fraenkel, *J. Amer. Chem. Soc.*, 1953, **75**, 4115) but, except possibly under such conditions, the above mechanism, like other homolytic mechanisms, is unlikely for the reasons already given (p. 3553).

as postulated here for thermal hydrogen transfer between hydroaromatic donors and quinones, are comparatively rare in organic chemistry. They normally occur only under the influence of reagents with a strong tendency to increase their covalency and to acquire a negative charge. Amongst inorganic reagents, certain metal halides, *e.g.*, aluminium chloride, display such properties, and steps involving transfer of hydride ion have been proposed for various reactions of Friedel–Crafts type (cf. Baddeley, Wrench, and Williamson, *J.*, 1953, 2112; Baddeley and Pickles, *ibid.*, p. 3726; Pines, Aristoff, and Ipatieff, *J. Amer. Chem. Soc.*, 1953, **75**, 4775); in most cases it is a positively charged carbonium ion formed under the agency of aluminium halides, rather than the halide



itself, which is regarded as the hydride-ion acceptor. Amongst primary organic reagents, the carbonyl group is ourstanding in conferring the required properties and the transfer of hydride ions has been postulated in the Cannizzaro reaction (cf. Alexander, " Principles of Ionic Organic Reactions," Wiley, New York, 1950) and in the reduction of ketones by metal alkoxides (Alexander, *op. cit.*; cf. Jackman and Macbeth, *J.*, 1952, 3252; Doering and Ashner, *J. Amer. Chem. Soc.*, 1953, **75**, 393), Grignard reagents (cf. Mosher and LaCombe, *ibid.*, 1950, **72**, 3994, 4991; Percival, Wagner, and Cook, *ibid.*, 1953, **75**, 3731), and metal hydrides (Trevoy and W. G. Brown, *ibid.*, 1949, **71**, 1675; H. C. Brown and Mead, *ibid.*, 1953, **75**, 6267). The azomethine group is less effective, but transfer of hydride ion has been suggested in the Sommelet and certain other reactions involving methyleneimines (Angyal, Penman, and Warwick, *J.*, 1953, 1742). Quinones, quinone imides, and similar compounds are exceptional, in not only possessing two suitable functional groups, but also acquiring increased resonance stabilisation through the addition of hydrogen. Thus, it is not altogether surprising that such compounds appear to represent neutral acceptors *par excellence* for hydride ion.

Experimental

Materials.—1 : 4-Dihydronaphthalene, prepared by Bamberger and Lodter's method (*Ber.*, 1887, **20**, 1705), was purified through its addition compound with mercuric acetate (m. p. 121°; Sand and Gennsler, *Ber.*, 1903, **36**, 3705) and had m. p. 25·5°; it was stored *in vacuo* at 0°. 9 : 10-Dihydroanthracene, m. p. 109°, was prepared by Wieland's method (*Ber.*, 1912, **45**, 492).

The quinones were prepared according to the following procedures and were purified by crystallisation from light petroleum (b. p. 60—80°) (cf. Braude, *J.*, 1945, 490) unless otherwise stated. 1 : 4-Benzoquinone (Underwood and Walsh, *Org. Synth.*, Coll. Vol. II, p. 553), m. p. 113°; chloro-1 : 4-benzoquinone (Levy and Schultz, *Annalen*, 1881, **210**, 138), m. p. 57°; 2 : 6-dichloro-1 : 4-benzoquinone (Conant and Fieser, *J. Amer. Chem. Soc.*, 1923, **45**, 2194), m. p. 121°; trichloro-1 : 4-benzoquinone (Knapp and Schultz, *Annalen*, 1881, **210**, 174), purified by sublimation, m. p. 169°; tetrachloro-1 : 4-benzoquinone, commercial sample crystallised from benzene, m. p. 286—287°; toluquinone (Clark, *Amer. Chem. J.*, 1892, **14**, 553), m. p. 68°; 2 : 5-dimethyl-1 : 4-benzoquinone (Nölting, Witt, and Forel, *Ber.*, 1885, **18**, 2667), m. p. 124°; 2 : 6-dimethyl-1 : 4-benzoquinone (Nölting and Forel, *ibid.*, p. 2673), m. p. 71—72°; 2-methyl-5-*iso*propyl-1 : 4-benzoquinone (Kremers, Wakeman, and Hixon, *Org. Synth.*, Coll. Vol. I, 2nd edn., p. 511), m. p. 45°; 1 : 2-naphthaquinone (Fieser, *ibid.*, Coll. Vol. II, p. 430), purified by sublimation, m. p. 146° (decomp.); 1 : 4-naphthaquinone (Braude and Fawcett, *J.*, 1951, 3117; *Org. Synth.*, **33**, 50), m. p. 124°; 9 : 10-phenanthraquinone (Underwood and Kochmann, *J. Amer. Chem. Soc.*, 1924, **46**, 2069), m. p. 204°.

Phenetole was refluxed over sodium and then distilled; it had b. p. 170°, n_D^{20} 1·5085. Diethylene glycol diethyl ether and decalin were similarly purified. *o*-Dichlorobenzene and dimethylformamide were fractionated. Nitrobenzene was dried over phosphoric oxide, distilled, and finally purified by fractional freezing, to m. p. 5·7° (Cohen and Bockhorst, *Z. physikal. Chem.*, 1934, *B*, **24**, 241). Propionic acid was refluxed over chromic oxide and fractionated from boron tripropionate (Eichelberger and LaMer, *J. Amer. Chem. Soc.*, 1933, **55**, 3633).

Isolation of Reaction Products.—(i) 1 : 4-Dihydronaphthalene (1·0 g.), benzoquinone (0·83 g.), and diethylene glycol diethyl ether (50 ml.) were heated in a sealed tube for 72 hr. at 131°. The mixture was then poured into water (250 ml.). An oil separated, which rapidly solidified and was filtered off. The crude material (0·91 g.) showed $\lambda_{max.}$ 2200 Å, $E^{1\%}_{1\,cm.}$ 8200 in EtOH, corresponding to a naphthalene content of 96% and a total yield of 87%. Recrystallisation from aqueous ethanol raised the m. p. to 79°, undepressed on admixture with naphthalene.

(ii) In a similar experiment with chloranil (0·12 g.) in phenetole (10 ml.), tetrachloroquinol (0·11 g.) separated on cooling of the reaction mixture.

(iii) 1 : 4-Dihydronaphthalene (1·30 g.), 1 : 2-naphthaquinone (1·58 g.), and toluene (100 ml.) were heated in a sealed tube for 48 hr. at 100°. On cooling, a purple solid (0·41 g.), m. p. 165—168°, separated and was filtered off. A further quantity (0·15 g.) of this material, presumably a mixture of the oxidation products known to be readily formed from 1 : 2-dihydroxynaphthalene (Stenhouse and Groves, *Annalen*, 1878, **194**, 208; Straus, Bernoully, and Mautner, *ibid.*, 1925, **444**, 165) was precipitated on dilution of the filtrate with pentane (100 ml.). The solution was then worked up as above, giving naphthalene picrate (2·9 g., 80%), m. p. 148—149°.

(iv) 1 : 4-Dihydronaphthalene (1·30 g.), 9 : 10-phenanthraquinone (2·08 g.), and chlorobenzene (100 ml.) were heated in a sealed tube for 6 days at 100°. On cooling and dilution with pentane, 9 : 10-dihydroxyphenanthrene, contaminated with a little unchanged quinone, separated and was filtered off; the m. p. was 142—145° (the pure quinol has m. p. 147°). The filtrate was worked up as above, giving naphthalene picrate (3·10 g., 86%), m. p. 148—149°.

Kinetic Experiments. General Procedures.—The ease of aerial oxidation of the quinol varies greatly from compound to compound and with the temperature. Oxidation could be rigorously prevented by a sealed-ampoule technique, but this is tedious and was only employed with quinones of low potential ($E^\circ < 0{\cdot}6$ v) where it is essential. With quinones of higher potential, more convenient procedures usually proved adequate and two different general methods with individual variations were therefore adopted.

Method 1. The reactions were carried out in long-necked flasks of the type described by Braude, Jones, and Stern (*J.*, 1946, 396) but provided with cold-fingers containing a narrow, central, inlet tube through which a very slow stream of dry nitrogen [purified by successive washing with alkaline pyrogallol, with sodium anthraquinone-2-sulphonate and sodium dithionite (hydrosulphite), and with sulphuric acid] could be passed. The nitrogen pressure was controlled by a simple mercury-filled overflow-valve and adjusted to *ca.* 0·5 cm. above atmospheric pressure; under such conditions slow outward leakage of nitrogen occurs, without the cold-fingers being "lifted" out of their seats. For runs up to 100°, thermostatic control was effected by means of an oil-bath controlled within ±0·05°. For runs at higher temperatures, jacketed vessels adapted from an earlier design (Waight, Thesis, London, 1950) were employed. The outer bulb was half-filled with the jacketing liquid and a few porcelain chips, and was heated to slow reflux with an electric mantle. For adequate temperature control, it was important that the outer bulb should be pear-shaped, that the inner bulb should be at least 3 cm. above the level of the liquid, and that the latter should be at least 2 cm. above the level of the heating mantle. The jacketing liquids used and the approximate temperatures measured in the inner bulbs were: methyl*cyclo*hexane (101°), toluene (110°), ethyl *n*-butyrate (119°), *iso*amyl alcohol (131°), xylene (141°), anisole (155°). The operational temperatures could be adjusted over a range of 0·5° by altering the temperature of the heating mantle, but were constant within ±0·1° for prolonged periods once equilibrium had been attained and provided fluctuations in atmospheric pressure did not exceed 20 mm.

Before a run was carried out, the empty vessel was flushed with nitrogen by slightly raising the cold-finger. A solution of dihydronaphthalene (or quinone) in phenetole or other solvent (usually 25 ml., 0·1M) was then introduced and the cold-finger was replaced. (In this and subsequent operations, the cold-finger was never completely removed, so that a nitrogen atmosphere was continuously maintained in the flask.) After thermal equilibrium had been attained (*ca.* 2 hr.), a small, open, glass capsule containing the finely ground quinone (or hydrocarbon) was dropped into the flask which was immediately shaken vigorously until all the

quinone had dissolved (this normally required *ca.* 30 sec.). Subsequently, 1 ml. samples were withdrawn at appropriate intervals by means of a long-stem graduated pipette and titrated, as described below.

Method 2. In this method, 1-ml. aliquot portions of reaction mixture were placed in ampoules at room temperature, and the ampoules were sealed after evacuation (to 10 mm.) in such a manner that only *ca.* 0·2 ml. of free space remained. All the ampoules were then placed simultaneously into an oil-bath or in a jacketed vessel similar to that used in method 1, and, at appropriate intervals, were removed and rapidly cooled. A correction was applied to the reaction time to allow for the initial period during which the ampoules attained thermal equilibrium. The maximum correction needed was 4 min.; fortunately the reactions with quinones of low potential are relatively slow, so that the necessary corrections were small compared with the reaction half-times.

Estimation of Quinones and Quinols.—(*a*) One ml. of reaction mixture was introduced into a 10-ml. glass-stoppered conical flask, either by pipetting or by crushing a sealed glass ampoule (washed free from jacketing liquid) with a glass rod which was then rinsed with a little phenetole. The appropriate amount of titanous chloride (2—3 ml., *ca.* 0·1N) was then added from an enclosed, self-filling burette in which the reagent was stored under hydrogen. Water (1 ml.) and the indicator were added and the stoppered flask was shaken until the colour of the indicator disappeared. The excess of titanous chloride was then estimated by back-titration with ferric ammonium sulphate solution (*ca.* 0·04N) until the colour of the indicator was no longer discharged by shaking. Generally the value of the back-titre was known approximately and it was found desirable to add immediately all but 0·2 ml. of the required volume so as to reduce the chance of aerial oxidation. Methylene-blue (1% in methanol) was employed as an indicator for quinones with potentials greater than 0·55 v and rosinduline (0·1% in methanol) or phenosafranine (0·1% in methanol) for quinones with potentials below this value. Titrations with rosinduline and phenosafranine were rendered tedious by the slow rate of reaction of the indicators with titanous chloride. The titanous chloride solution required daily standardisation against the ferric ammonium sulphate solution.

(*b*) One ml. of the reaction mixture, acetic acid (1 ml.), water (2 ml.), and one drop of 0·1% sodium diphenylaminesulphonate were placed in a glass-stoppered, 10-ml. conical flask, and ceric ammonium sulphate solution (*ca.* 0·04N) was run in slowly from a burette with constant shaking, until a permanent violet colour persisted on shaking for ½ min. The method is general for 1 : 4-quinones and an accuracy of 1% or better is readily obtained, provided high local concentrations of reagent, which slowly attacks the quinones, are avoided. 1 : 2-Quinols cannot generally be estimated by this method as the quinones readily undergo further oxidation, but with 9 : 10-dihydroxyphenanthrene it was just possible to obtain a " flash " end-point.

(*c*) These titrations were performed as described in method (*a*) except that ceric ammonium sulphate was used as the back-oxidant. When the first end-point was reached, sodium diphenylaminesulphonate indicator and acetic acid (2 ml.) were added and the titration was continued as in method (*b*). The difference between the two titres should be equivalent to the initial concentration of the quinone provided quinol and naphthalene are the only reaction products.

Individual Runs.—One or more representative runs are recorded below for each quinone, so as to illustrate the procedures selected in different cases, the accuracies attained, and the various types of deviations from second-order kinetics which are encountered. Concentrations of quinone (*a*) and hydrocarbons (*b*) are 0·1M unless otherwise stated. x = ml. of reagent. Second-order rate constants k are given in l. mole^{-1} min.$^{-1}$; the values differ from those in the Tables which are in different units. The precision index employed is the standard deviation of the mean.

(i) Benzoquinone in phenetole at 100°.
Method 1*b*. $[Ce^{4+}] = 0{\cdot}0452$N.

t (min.)	118	180	287	396	427	1458
x	0·35	0·51	0·76	0·96	1·06	2·29
10^2k	0·727	0·722	0·722	0·700	7·35	0·735

$10^2k = 0{\cdot}723 \pm 0{\cdot}005$

(ii)—(iv) Benzoquinone in phenetole at 100°.

a	0·050	0·100	0·200
b	0·100	0·050	0·100
10^2k	0·701 ± 0·013	0·710 ± 0·008	0·705 ± 0·010

(v) Benzoquinone in phenetole at 131°.

Method 1*c*. 2 ml. of 0·0995N-$TiCl_3$ back-titrated with 0·0467N-Ce^{4+}. x' refers to the second end-point.

t (min.)	0	27·6	43·6	68·5	112	143	182	224	301	680	2650
x	0·02	0·60	0·76	1·05	1·54	1·78	2·04	2·29	2·62	3·37	4·12
x'	4·31	4·82	5·04	5·31	5·82	6·03	6·35	6·60	6·86	7·61	8·32
$x' - x$	4·29	4·22	4·28	4·26	4·28	4·25	4·31	4·31	4·24	4·24	4·20
Reaction (%)	—	11·9	17·3	23·3	35·2	40·1	47·5	53·4	59·5	77·0	93·5
10^2k	—	4·90	4·74	4·44	4·85	4·68	4·98	5·10	4·87	4·90	—

$10^2k = 4·83 \pm 0·07$

(vi) Toluquinone in phenetole at 131°.

Method 1*b*. $[Ce^{4+}] = 0·0445$N.

t (min.)	77	96	120	161	214	295	309	410	1358
x	0·58	0·70	0·85	1·09	1·31	1·66	1·70	2·02	3·29
10^2k	1·93	1·92	1·94	1·98	1·92	1·99	1·97	1·99	2·00

$10^2k = 1·96 \pm 0·02$

(vii) Chloro-1 : 4-benzoquinone in phenetole at 90·0°.

Method 1*b*. $[Ce^{4+}] = 0·0465$N.

t (min.)	64·5	146	210	310	447	537	754
x	0·37	0·74	0·98	1·31	1·70	1·85	2·22
10^2k	1·46	1·42	1·41	1·41	1·46	1·41	1·43

$10^2k = 1·42 \pm 0·01$

(viii) 2 : 6-Dichloro-1 : 4-benzoquinone in phenetole at 119°.

Method 1*b*. $[Ce^{4+}] = 0·0465$N. This run illustrates the marked deviations from second-order kinetics observed with this quinone.

t (min.)	9	19	30	52	65	122
x	0·60	1·14	1·42	1·80	1·98	2·43
10^2k	23·9	19·0	16·5	13·9	13·1	10·7

(ix) 2 : 6-Dichloro-1 : 4-benzoquinone in phenetole at 80·2°.

Method 1*b*. $[Ce^{4+}] = 0·0465$N. This run illustrates that second-order kinetics are observed with this quinone during the first 10% of the reaction (cf. previous run).

t (min.)	19	25	30	35	40	46	52	59
x	0·14	0·18	0·22	0·25	0·29	0·32	0·37	0·39
10^2k	1·77	1·75	1·80	1·77	1·81	1·75	1·81	1·70

$10^2k = 1·79 \pm 0·02$ (up to 52 min.)

(x) Trichloro-1 : 4-benzoquinone in phenetole at 69·8°.

Method 1*b*. $[Ce^{4+}] = 0·0465$N.

t (min.)	17	34	54	78	100	126	158	221
x	0·06	0·125	0·17	0·265	0·34	0·41	0·49	0·61
10^2k	0·833	0·880	0·762	0·842	0·860	0·877	0·815	0·750

$10^2k = 0·837 \pm 0·030$ (up to 158 min.)

(xi) Tetrachloro-1 : 4-benzoquinone in phenetole at 100·5°.

Method 1*b*. $[Ce^{4+}] = 0·0455$N.

t (min.)	66·5	85	111	122	144·5	178	250
x	1·82	2·05	2·31	2·45	2·68	2·84	3·15
10^2k	10·03	10·03	10·00	10·03	10·08	10·03	10·02

$10^2k = 10·03 \pm 0·01$

(xii) 2 : 6-Dimethyl-1 : 4-benzoquinone in phenetole at 154·5°.

Method 2*b*. $[Ce^{4+}] = 0·0484$N. This run illustrates the upward drift in k due to product catalysis.

t (min.)	46	94	126	153	212	264	330	370
x	0·505	1·00	1·23	1·44	1·83	2·09	2·37	2·53
10^2k	3·03	3·40	3·37	3·50	3·76	3·88	4·08	4·27

$10^2k = 3·07$ (graphical extrapolation)

(xiii) 2 : 5-Dimethyl-1 : 4-benzoquinone in phenetole at 140·8°.

Method 2*b*. $[Ce^{4+}] = 0{\cdot}0465$N. This run illustrates the upward drift in k due to product catalysis.

t (min.)	67	136	228	310	420	505	1522	3208
x	0·24	0·46	0·74	0·94	1·20	1·42	2·85	3·60
10^2k	0·882	0·881	0·913	0·904	0·920	0·975	1·32	1·61

$10^2k = 0{\cdot}88$ (graphical extrapolation)

(xiv) Thymoquinone in phenetole at 100·0°.

Method 2*b*. $[Ce^{4+}] = 0{\cdot}0484$N.

t (min.)	1190	2695	4050	5385	6805	8220
x	0·18	0·40	0·62	0·84	1·05	1·25
10^2k	0·0383	0·0398	0·0437	0·0474	0·0500	0·0528

$10^2k = 0{\cdot}038$ (graphical extrapolation)

(xv) Thymoquinone in phenetole at 154°.

Method 2*b*. $[Ce^{4+}] = 0{\cdot}0484$N. Comparison with run (xiv) illustrates the decrease in product catalysis with increasing temperature.

t (min.)	80	162	240	301	399
x	0·49	0·85	1·25	1·47	1·79
10^2k	1·68	1·62	1·82	1·84	1·92

(xvi) Thymoquinone in phenetole at 154°. Concentration of reactants, 0·2M.

Method 2*b*. $[Ce^{4+}] = 0{\cdot}0484$N. Comparison with run (xv) illustrates the increase with reagent concentration of the upward drift due to product catalysis. α is defined by the equation $k_2 = (1/\alpha t) \ln [a(a - x - \alpha)/(a + \alpha)(x - a)]$ (see p. 3550) which is clearly not obeyed.

t (min.)	80	162	240	301	399
x	1·77	3·10	4·10	4·66	5·36
10^2k	1·70	1·86	2·06	2·16	2·32
α	0·17	2·0	2·4	2·5	2·9

(xvii) Thymoquinone in nitrobenzene at 155·5°.

Method 2*b*. $[Ce^{4+}] = 0{\cdot}0465$N. In this solvent product catalysis is absent, at least over the first half of the reaction.

t (min.)	40	63	80	100	120	182	333
x	0·52	0·70	0·89	1·05	1·20	1·59	2·24
10^2k	3·44	3·09	3·27	3·23	3·23	3·22	3·27

$10^2k = 3{\cdot}25 \pm 0{\cdot}04$

(xviii) Thymoquinone in 0·120M-thymoquinol in phenetole at 155·0°.

Method 2*b*. $[Ce^{4+}] = 0{\cdot}0484$N.

t (min.)	0	43	75	134	182	249
x	4·96	5·45	5·86	6·30	6·67	7·07
10^2k	3·14	3·72	3·60	3·69	3·90	4·20

$10^2k = 3{\cdot}30$ (graphical extrapolation)

(xix) Thymoquinone in 0·058M-*p*-nitrophenol in phenetole at 155°.

Method 2*b*. $[Ce^{4+}] = 0{\cdot}0465$N.

t (min.)	15	30	60	90	105	120	135	210
x	0·28	0·48	0·79	1·08	1·17	1·29	1·39	1·70
10^2k	3·60	3·81	3·71	3·72	3·74	3·74	3·74	3·37

$10^2k = 3{\cdot}68 \pm 0{\cdot}05$

(xx) Thymoquinone in 0·058M-*p*-nitroanisole in phenetole at 155·4°.

Method 2*b*. $[Ce^{4+}] = 0{\cdot}0465$N.

t (min.)	76	118	134	183	235	275	348
x	0·52	0·77	0·86	1·09	1·34	1·50	1·78
10^2k	1·81	1·85	1·87	1·85	1·93	1·96	2·08

$10^2k = 1{\cdot}75$ (graphical extrapolation)

(xxi) Thymoquinone in 0·058M-picric acid in phenetole at 155·0°.

Method 2*b*. $[Ce^{4+}] = 0·0465$N.

t (min.)	11	29	63	135	249	382
x	0·10	0·21	0·40	0·60	0·75	0·80
10^2k	2·16	1·96	1·63	1·20	0·85	0·60

$10^2k = 2·2$ (graphical extrapolation)

(xxii) Thymoquinone in phenetole containing 0·0045M-benzoyl peroxide at 154·6°.

Method 2*b*. $[Ce^{4+}] = 0·0484$N.

t (min.)	116	140	178	243	337
x	0·66	0·80	0·96	1·25	1·57
10^2k	1·64	1·72	1·71	1·79	1·83

$10^2k = 1·60$ (graphical extrapolation)

(xxiii) Thymoquinone in propionic acid at 141·1°.

Method 2*b*. $[Ce^{4+}] = 0·0465$N.

t (min.)	30	42	70	90	120	165	210	255	391	468
x	0·23	0·32	0·48	0·62	0·78	1·04	1·22	1·49	1·81	1·96
10^2k	1·90	1·92	1·80	1·87	1·85	1·93	1·89	2·08	1·86	1·79

$10^2k = 1·90 \pm 0·04$

(xxiv) Thymoquinone in 90% (v/v) aqueous propionic acid at 141·1°.

Method 2*b*. $[Ce^{4+}] = 0·0465$N.

t (min.)	20	40	125	173	240	290
x	0·24	0·45	1·16	1·31	1·89	2·08
10^2k	2·96	2·92	2·96	3·13	3·27	3·23

$10^2k = 3·09 \pm 0·07$

(xxv) Thymoquinone in 0·07M-perchloric acid in propionic acid at *ca.* 23·4°.

Method 2*b*. $[Ce^{4+}] = 0·0465$N.

t (min.)	117	262	395	1380
x	0·26	0·38	0·45	0·57
10^2k	0·55	0·37	0·30	0·11

(xxvi) Thymoquinone and 9 : 10-dihydroanthracene in propionic acid at 141·0°.

Method 2*b*. $[Ce^{4+}] = 0·0465$N.

t (min.)	120	209	337	424	956	1053	1170	1292
x	0·28	0·47	0·79	0·95	1·82	1·89	1·92	2·12
10^2k	0·581	0·589	0·569	0·670	0·760	0·745	0·690	0·752

$10^2k = 0·58$ (graphical extrapolation)

(xxvii) Thymoquinone and 9 : 10-dihydroanthracene in propionic acid containing trichloroacetic acid (1·0M) at 141·0°.

Method 2*b*. $[Ce^{4+}] = 0·0465$N.

t (min.)	45	77	156	219	285
x	0·25	0·40	0·75	1·04	1·24
10^2k	1·37	1·34	1·36	1·45	1·42

$10^2k = 1·36$ (graphical extrapolation)

(xxviii) 1 : 4-Naphthaquinone in phenetole at 132·0°.

Method 2*b*. $[Ce^{4+}] = 0·0484$N.

t (min.)	150	322	388	940	1400	3140	5250
x	0·06	0·12	0·145	0·40	0·61	0·89	1·11
10^2k	0·099	0·094	0·097	0·114	0·123	0·088	0·070

Further readings were impossible as the end-point was obscured by a coloured by-product.

(xxix) Isomerisation of 1 : 4-dihydroxynaphthalene (0·05M) in phenetole at 131°.
Method 2*b*. $[Ce^{4+}] = 0·0439$N.

t (min.)	0	990	1800	7550
x	2·28	1·79	1·68	1·70

(xxx) 1 : 2-Naphthaquinone in phenetole at 99·8°.
Method 2*a*. 3 Ml. of 0·0804N-$TiCl_3$ back-titrated with 0·0552N-Fe^{3+}.

t (min.)	0	61	89	152	214	283	314
x	0·73	1·61	2·01	2·69	3·25	3·70	3·76
10^2k	—	5·20	6·04	7·65	8·70	11·5	16·2

(xxxi) 1 : 2-Naphthaquinone in phenetole at 70·0°.
Method 2*a*. 3 Ml. of 0·0723N-$TiCl_3$ back-titrated with 0·0545N-Fe^{3+}.

t (min.)	0	62	80	100	121	140	180
x	0·30	0·57	0·64	0·74	0·80	0·91	1·09
10^2k	—	1·26	1·24	1·34	1·29	1·42	1·51

$10^2k = 1·26$ (graphical extrapolation)

(xxxii) 9 : 10-Phenanthraquinone in phenetole at 122·0°.
Method 2*b* (flash end-point). $[Ce^{4+}] = 0·0484$N.

t (min.)	33	60	114	200	248	309	360
x	0·22	0·41	0·84	1·55	1·84	2·16	2·40
10^2k	1·71	1·83	2·24	3·00	3·24	3·56	3·86

(xxxiii) 9 : 10-Phenanthraquinone in phenetole at 99·6°.
Method 2*b* (flash end-point). $[Ce^{4+}] = 0·0484$N.

t (min.)	80	106	121	151	180	214
x	0·14	0·17	0·22	0·28	0·33	0·39
10^2k	0·439	0·405	0·465	0·464	0·483	0·489

$10^2k = 0·422$ (graphical extrapolation)

Arrhenius energies of activation E_A were calculated by the method of least squares; they are estimated to be accurate to $\pm 0·1$—0·4 kcal. in most cases, but with 1 : 2-naphthaquinone and 9 : 10-phenanthraquinone the spread of individual values was somewhat greater. Entropies of activation $\Delta S^{\ddagger}$ were calculated from the equation $\log k = \log (e\boldsymbol{RT}/\boldsymbol{Nh}) - E_A/2·3\boldsymbol{RT} + \Delta S^{\ddagger}/2·3\boldsymbol{R}$, E_A being expressed in cal./mole, and free energies of activation from $\log k = \log (\boldsymbol{RT}/\boldsymbol{Nh}) - \Delta G^{\ddagger}/2·3\boldsymbol{R}$.

The work described in this and the following paper was carried out during the tenure by one of us (L. M. J.) of a Beit Research Fellowship.

Department of Organic Chemistry,
Imperial College of Science and Technology,
South Kensington, London, S.W.7.

[*Received, February 24th*, 1954.]

Hydrogen Transfer. Part III. The Dehydrogenation of Hydroaromatic Hydrocarbons by Quinones. Quantitative Comparison of Donors.*

By E. A. Braude, L. M. Jackman, and R. P. Linstead.

[Reprint Order No. 5154.]

The dehydrogenations of four hydroaromatic donors by 1 : 4-benzoquinone and 1 : 2-naphthaquinone have been studied kinetically. The reactivities decrease in the sequence 1 : 4-dihydrobenzene > 1 : 4-dihydronaphthalene > 9 : 10-dihydroanthracene > 1 : 2-dihydronaphthalene. This sequence is explained in terms of the mechanism postulated in Part II * and is ascribed to the differences in the additional resonance stabilisation which accompanies the aromatisation of the donor.

In the preceding paper, the general features of the hydrogen transfer between 1 : 4-dihydronaphthalene and quinones, and the effects of structural variation in the acceptor, have been described. The present paper deals with a preliminary investigation of the effect of structural variation in the hydroaromatic donor.

The donors studied were 1 : 2- and 1 : 4-dihydrobenzene, 1 : 2- and 1 : 4-dihydronaphthalene, and 9 : 10-dihydroanthracene, mostly with 1 : 4-benzoquinone as acceptor. The reactions were followed by the experimental methods employed in Part II, and the results are summarised in the Table. Only an upper limit could be determined for the rate of dehydrogenation of 1 : 2-dihydrobenzene, as the main reaction which occurs is Diels–Alder addition of the quinone to the donor. The dehydrogenation of 9 : 10-dihydroanthracene was also complicated by a competitive Diels–Alder reaction, in this case between the quinone and the dehydrogenation product, anthracene; the second-order rate constants showed an upward or downward drift depending on whether the reaction was followed by disappearance of quinone or the appearance of quinol, and the values in the Table were obtained by extrapolating to zero time. No deviations from second-order kinetics were observed with 1 : 4-dihydrobenzene and 1 : 2-dihydronaphthalene.

*Rate constants for the dehydrogenation of various hydrocarbons by quinones.**

Donor	Acceptor	Solvent	Temp.	10^4k (l. mole^{-1} sec.$^{-1}$)
1 : 4-Dihydrobenzene	Benzoquinone	Dioxan	80°	0·28
1 : 2-Dihydrobenzene	,,	,,	,,	<0·02
1 : 4-Dihydronaphthalene ...	,,	,,	,,	0·16
1 : 2-Dihydronaphthalene ...	,,	,,	,,	0·0025
9 : 10-Dihydroanthracene ...	,,	,,	,,	0·042
1 : 4-Dihydronaphthalene ...	Benzoquinone	Anisole	131	10·5
1 : 2-Dihydronaphthalene ...	,,	,,	,,	0·066
9 : 10-Dihydroanthracene ...	,,	,,	,,	3·8
1 : 4-Dihydronaphthalene ...	Chloranil	Phenetole	110	78
9 : 10-Dihydroanthracene ...	,,	,,	,,	23
1 : 4-Dihydronaphthalene ...	Thymoquinone	Propionic acid	140	3·4
9 : 10-Dihydroanthracene ...	,,	,,	,,	0·97
1 : 4-Dihydronaphthalene ...	1 : 2-Naphthaquinone	Anisole	131	35
1 : 2-Dihydronaphthalene ...	,,	,,	,,	0·45

* 0·1M-Solutions of both reactants, except for 1 : 4-dihydrobenzene and 1 : 4-dihydronaphthalene at 80° which were 0·2M.

The results in the Table show that the ease of dehydrogenation of the donors decreases in the sequence 1 : 4-dihydrobenzene > 1 : 4-dihydronaphthalene > 9 : 10-dihydroanthracene > 1 : 2-dihydronaphthalene. The relative rates at 80° are approximately in the ratios 100 : 50 : 10 : 1 and are similar for benzoquinone, chloranil, and thymoquinone.

Theoretically one of the main factors controlling the sequence of reactivities of the donors will be the gain in resonance energy (ΔE_R) accompanying aromatisation of the donor, which is bound to assist the reaction just as does the gain in resonance energy in the acceptor (Part II). The approximate values of ΔE_R for 1 : 4-dihydrobenzene, 1 : 4-dihydronaphthalene, 1 : 2-dihydronaphthalene, and 9 : 10-dihydroanthracene are 36, 30, 25, and

* Part II, preceding paper.

20 kcal., based on the following experimental resonance energies: 1 : 4-dihydrobenzene, 0(assumed) *; benzene, 36 (Kistiakowsky, Ruhoff, Smith, and Vaughan, *J. Amer. Chem. Soc.*, 1936, **58**, 147; cf. Klages, *Ber.*, 1949, **82**, 358); 1 : 4-dihydronaphthalene, 37 (Williams, *J. Amer. Chem. Soc.*, 1942, **64**, 1395); 1 : 2-dihydronaphthalene, 42; naphthalene, 67 (Klages, *loc. cit.*); 9 : 10-dihydroanthracene, 77; anthracene 97 (Magnus and Becker, *Erdöl and Kohle*, 1951, **4**, 115). Thus, for the three 1 : 4-dihydro-derivatives at least, the sequence of resonance-energy gains is the same as the sequence of reactivities and a roughly linear relation exists between log k and ΔE_R. 1 : 2-Dihydronaphthalene is somewhat less reactive than expected on this basis, an anomaly probably related, at least in part, to the non-equivalence of the 1- and the 2-hydrogen atoms.

If the entropies of activation are assumed to be approximately constant, the relative rates of the four hydrocarbons correspond to increases in the heats and free energies of activation of about 0·4, 1·2, and 2 kcal. relative to 1 : 4-dihydrobenzene. These differences are much smaller than those in ΔE_R and although the present measurements are insufficient to yield an accurate relation, it is instructive to express them in the form of relation (1)† which connects $\Delta G^{\ddagger}$ for a single acceptor (benzoquinone) with the resonance-energy gains of different donors:

$$\Delta G^{\ddagger} = 29{\cdot}6 - 0{\cdot}1\Delta E_R \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

This may be compared with the relation (2) previously deduced (Part II) between $\Delta G^{\ddagger}$ for a single donor (1 : 4-dihydronaphthalene) and the free-energy gains of different acceptors:

$$\Delta G^{\ddagger} = 38{\cdot}0 - 0{\cdot}071\Delta G^{\circ} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Both relations are of the same form and indicate that the energy of activation is made up of two parts of opposite sign. One part, the intercept of the plots on the $\Delta G^{\ddagger}$ axis, represents the energy required to stretch the C–H bond in the donor from its normal distance to that in the transition state and is approximately constant. [The numerical values of the intercepts in relations (1) and (2) are not comparable, because ΔG° includes the bond energy changes whereas ΔE_R does not.] The other part, which is variable, and controls the slope of the plots, represents the driving force provided by the resonance energy gains in the products. It is almost certainly no coincidence that the slopes of the straight lines represented by relations (1) and (2) have nearly identical values; they indicate that, in the transition state, aromatic character and additional resonance stabilisation are developed to a small and roughly equal extent (*ca.* 10%) in both donor and acceptor.

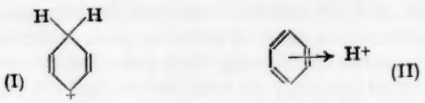
The results are in accord with a two-step mechanism (2) of the type proposed in Part II and may be regarded as additional evidence against the one-step mechanism (1) involving a pseudocyclic transition state, which was previously considered and rejected for other reasons; in such a transition state, aromatic character should be highly developed and resonance stabilisation should amount more nearly to 50% than to 10% of that in the final products. The same objection applies, though less forcibly, to a one-step mechanism involving a linear transition state and differing from (2) in that the transfer of one hydrogen atom (in the form of a proton) to a solvent molecule would be synchronised with the transfer of the other hydrogen atom (in the form of a hydride ion) to the quinone acceptor. The problem of distinguishing between such one-step and two-step mechanisms is rather analogous to the question whether or not the ejection of a proton is kinetically significant in electrophilic aromatic substitution (cf. Braude, *Ann. Reports*, 1949, **46**, 131 and references there cited); like the latter it could be conclusively resolved by studying the effects of isotopic substitution, although the interpretation of the results would be more complicated owing to the circumstance that a hydrogen atom is involved in both the presumed steps in the transfer reaction instead of in only one in the substitution reaction. Fortunately, such experiments seem hardly necessary, for, apart from the present evidence, the synchronised removal of the proton by the solvent is rendered extremely unlikely by the fact (Part II) that dehydrogenation proceeds with comparable facility in phenetole and decalin although

* 1 : 4-Dihydrobenzene will have a small resonance energy arising from hyperconjugation, but this is unlikely to exceed 3 kcal. and does not affect the present argument.

† Relation (1) is not a strict thermodynamic equation since the so-called resonance energies are really enthalpies and not free energies, but this does not significantly affect the present argument.

the latter solvent must be practically devoid of proton-acceptor properties. Presumably, in such a solvent, the proton is removed directly by a quinol anion, when the transfer of the hydride ion is complete.

If the conclusion that the transfers of the two hydrogen atoms are kinetically independent is accepted, the existence of a semiquantitative correlation between the reactivity and resonance-energy gain of donors permits elaboration of the two-step mechanism. This mechanism postulates the formation, in the rate-determining step, of the conjugate acid of the aromatic hydrocarbon ($R{\cdot}H^+$), but the precise nature of this intermediate has so far been purposely left undefined. Two possibilities can be envisaged. In the first, one of the two reactive carbon–hydrogen bonds in the donor remains substantially unchanged during the rate-determining step, and the intermediate is a true carbonium ion (*e.g.*, I); an alternative designation which emphasises the retention of ordinary single-bond character in the CH_2 group is " σ-complex " (Brown and Pearsall, *J. Amer. Chem. Soc.*, 1952, **74**, 191; Brown and Brady, *ibid.*, p. 3570; Brown and Wallace, *ibid.*, 1953, **75**, 6268). In the second, both the reactive carbon–hydrogen bonds in the donor undergo more or less synchronised changes, but whereas one hydrogen atom is actually transferred to the quinone acceptor in the form of a hydride ion, the other hydrogen atom is not subject to any marked nuclear displacement and remains within the orbit of the donor although the electronic nature of its attachment to the carbon skeleton is altered; the hybridisation of all the carbon atoms then changes simultaneously from sp^3 to sp^2 and the intermediate represents a π-complex (*e.g.*, II) (cf. Dewar, *J.*, 1946, 406; *Discuss. Faraday Soc.*, 1947, **2**, 50; " Electronic Theory of Organic Chemistry," Oxford Univ. Press, 1949). The distinction between the σ-complex and the π-complex type of intermediates, which are extremes of a continuous range (cf. Mulliken, *J. Phys. Chem.*, 1952, **56**, 801), is based on the following consideration: The gain in resonance stabilisation in converting a dihydro-compound into a σ-complex such as (I) will be derived mainly from charge-resonance and would be expected to increase in



(I) (II)

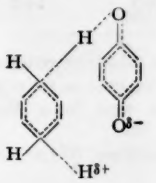
the sequence benzene<naphthalene<anthracene, as can be seen by considering, for example, the number of resonance forms (3, 7, and 16, respectively). Hence, on this hypothesis, the reactivities should increase in the same order, dihydrobenzene<dihydronaphthalene<dihydroanthracene, which is the reverse of that observed.* On the other hand, the resonance stabilisation of π-complexes such as (II) will increase in the same order as that of the aromatic hydrocarbons from which they are derived (cf. Dewar, *loc. cit.*); and the sequence of resonance-energy gains predicted on this hypothesis therefore agrees with that observed, dihydrobenzene>dihydronaphthalene>dihydroanthracene.

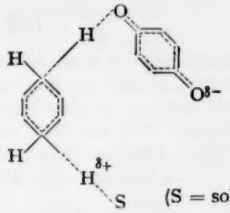
The conclusion that the intermediates $R{\cdot}H^+$ in hydrogen transfer by mechanism (2) are π- rather than σ-complexes is in harmony with the somewhat fragmentary evidence at present available concerning the range of existence of these limiting types of species in different environments. Sufficient is known to indicate that the bond type is strongly influenced by the nature of the anions and other proton-acceptors with which the species $R{\cdot}H^+$ is in equilibrium; weakly basic surroundings favour a σ-complex, while strongly basic surroundings favour a π-complex. Thus, it has been demonstrated spectroscopically that anthracene in sulphuric–acetic acid (a strongly proton-donating, extremely weakly basic medium) is converted predominantly into the σ-complex in which a proton is attached and localised at the 9-position (Gold and Tye, *J.*, 1952, 2172); similarly, benzenoid hydrocarbons are converted into σ-complexes under the combined influence of hydrogen chloride and aluminium chloride, because the anion $AlCl_4^-$ is very weakly basic (Brown and Brady, *loc. cit.*). On the other hand, hydrogen chloride alone appears to convert benzenoid hydrocarbons into π-complexes. This is indicated (Brown and Brady, *loc. cit.*) by the much closer relative basicities of toluene, *o*-xylene, and *m*-xylene towards HCl (1·00, 1·23, and 1·37, respectively) than towards $HAlCl_4$ (1, 200, and 2000, respectively); unlike $AlCl_4^-$,

* The same applies to mechanisms involving free-radical intermediates RH· (cf. Part II, *loc. cit.*).

the more strongly basic anion Cl^- can compete effectively with the hydrocarbon for a proton, and the π-complex can be regarded as a hydrogen-bonded ion-pair, $R \ldots H^+ \ldots Cl^-$. Now, in hydrogen transfer from a hydroaromatic donor to a quinone, the intermediate $R{\cdot}H^+$ is generated simultaneously with a strongly basic quinol anion QH^- which provides precisely the type of environment conducive to π-complex formation; even if the distance between the hydrogen atom in $R{\cdot}H^+$ and the charged oxygen atom in QH^- considerably exceeds the covalent-bond length, it will still be well within the range of electrostatic forces at the completion of the rate-determining step. We may thus further refine the formulation of the intermediate by representing it as $RH^+ \ldots QH^-$ in which an electrovalent bond exists between RH^+ and QH^-. The second, fast step then becomes the conversion of this electrovalent bond into a covalent one, to give $R + QH_2$. This implies that both hydrogen atoms are eventually transferred to the same quinone acceptor and the distinction between such a process and the one-step mechanism (1) considered in Part II is a subtle one, depending, as it does, on the detailed geometry of the transition states and the time-sequence of electron re-distributions as well as of nuclear displacements. Moreover, the degree of electrovalent interaction between the reactants will be influenced by the solvent and it is highly probable that in a strongly basic solvent such as phenetole the positive " end " of the transition state will be surrounded by solvent molecules which will intervene as acceptors. Under such conditions of indirect proton transfer, the proton need not necessarily go to the quinone molecule involved in the rate-determining step, but may be taken up by a different quinol anion. The unsolvated and solvated transition states of the rate-determining step are schematically represented in (III) and (IV); it has been assumed that the preferred H–O–C angle is about 120°, but that it is distorted to about 90° if there is strong attraction between the opposite ends of the transition state, as in (III). The actual configuration in a particular case will obviously depend not only on the solvent, but also on the electronic and steric properties of the donor and acceptor.

(III)





(IV)

(S = solvent)

One consequence of this model is that the geometrical correspondence between the labile hydrogen atoms in the donor and the oxygen atoms in the acceptor will have *some* influence on the ease of transfer, though less than predicted for the one-step mechanism (1) (Part II, *loc. cit.*, p. 3554). Such an effect is indicated by the differing ratios of the rate constants for the dehydrogenation of 1 : 4- and 1 : 2-dihydronaphthalene by 1 : 4-benzoquinone (160) and 1 : 2-naphthaquinone (80). An even smaller ratio would be expected with a quinone in which the two carbonyl functions are so far apart that the electrovalent interaction present in a transition state of type (III) is very weak; furthermore, with such a quinone, solvent effects would be expected to be relatively large. Work in progress with 1 : 8-diphenoquinones as acceptors (cf. Part IV) indicates that these expectations are fulfilled.

Experimental

Materials.—1 : 4-Dihydrobenzene, b. p. 81°/763 mm., n_D^{24} 1·4707, was prepared from benzene according to Wibaut and Haak (*Rec. Trav. chim.*, 1948, **67**, 85) and purified through its tetrabromide. 1 : 2-Dihydrobenzene, b. p. 80°/762 mm., n_D^{25} 1·4712, was prepared from *cyclo*hexene (Ziegler *et al.*, *Annalen*, 1942, **551**, 80; Arbusov and Mastryukova, *Izvest. Akad. Nauk U.S.S.R. Otdel. Khim. Nauk*, 1952, 665). Dioxan and anisole were purified by refluxing with sodium and fractionation. The other materials were those described in Part II (*loc. cit.*).

Isolation of Reaction Products.—(i) 1 : 2-Dihydronaphthalene (1·30 g.), 1 : 2-naphthaquinone (1·58 g.), and chlorobenzene (100 ml.) were refluxed under nitrogen for 8 days. On cooling, a purple solid (0·80 g.), m. p. 160—170° (cf. Part II), separated and was filtered off. The filtrate

was diluted with light petroleum (100 ml.; b. p. 40—60°), filtered again, and chromatographed on alumina, with more light petroleum (100 ml.) as an eluant. The combined solutions were concentrated by slow distillation through a column until the volume was 3 ml. This was treated with a hot, saturated solution of picric acid (2·3 g.) in ethanol, giving naphthalene picrate (2·15 g., 60%), m. p. 148—149°.

(ii) 9 : 10-Dihydroanthracene (1·8 g.), benzoquinone (2·16 g.), and phenetole (100 ml.) were heated under nitrogen for 60 hr. at 130°. The solution was then evaporated to dryness under reduced pressure and the residue extracted with hot water to remove quinol. There remained the anthracene–benzoquinone adduct which, after crystallisation from xylene, formed pale yellow needles (2·36 g., 82%) which sintered at 207° (cf. Clar, *Ber.*, 1931, **64**, 1676).

Kinetic Measurements.—These were carried out by the methods described in Part II. In most cases, method A was used (reduction of unchanged quinone with excess of titanous chloride, followed by back-titration with ferric ammonium sulphate). One typical run for each hydrocarbon is reproduced below. In each case, the stated volume of titanous chloride was added to 1 ml. of reaction mixture and x is the volume of ferric salt solution consumed. The limits of error of the second-order rate constants (k, l. mole^{-1} min.$^{-1}$) are given as standard deviations of the mean.

(i) 1 : 4-Dihydrobenzene (0·2M) and 1 : 4-benzoquinone (0·2M) in dioxan at 80°. 4 ml. of 0·0975 N-Ti^{3+} back-titrated with 0·0407N-Fe^{3+}.

t (min.)	0	123	244	339	420	1525
x (ml.)	0·06	0·41	0·80	1·09	1·20	2·95
10^4k	—	15·9	17·5	17·8	16·4	14·5

$10^4k = 16{\cdot}5 \pm 0{\cdot}6$

(ii) 1 : 2-Dihydrobenzene (0·1M) and 1 : 4-benzoquinone (0·1M) in dioxan at 80°. 2·5 ml. of 0·0970N-Ti^{3+} back-titrated with 0·0407N-Fe^{3+}.

t (min.)	0	120	225	315	1370
x (ml.)	1·25	1·99	2·48	2·70	4·36
10^4k	—	15·8	15·7	14·0	13·7

$10^4k = 14{\cdot}8 \pm 0{\cdot}8$

This rate constant refers almost entirely to the Diels–Alder addition reaction, for isolation of the products after 3 days at 100° gave an 86% yield of the adduct as pale yellow plates, m. p. 94—96°, raised to 97° by one recrystallisation (Diels, Alder, and Stein, *Ber.*, 1929, **62**, 2337; Alder and Stein, *Annalen*, 1933, **501**, 247, give m. p. 98°).

(iii) 1 : 4-Dihydronaphthalene (0·1M) and 1 : 4-benzoquinone (0·1M) in anisole at 130°. 5·0 ml. of 0·059N-Ti^{3+} back-titrated with 0·0509N-Fe^{3+}.

t (min.)	0	16·3	32	38	47	58	96
x (ml.)	1·99	2·34	2·66	2·72	2·90	2·99	3·35
10^4k	—	61·8	67·1	61·1	66·2	61·4	58·2

$10^4k = 64 \pm 0{\cdot}2$

(iv) 1 : 2-Dihydronaphthalene (0·1M) and 1 : 4-benzoquinone (0·1M) in anisole at 130°. 2·5 ml. of 0·0970N-Ti^{3+} back-titrated with 0·0407N-Fe^{3+}.

t (min.)	0	1230	8380	11,500	14,400
x (ml.)	1·16	1·42	2·36	2·61	3·00
10^4k	—	4·36	4·00	3·98	4·20

$10^4k = 4{\cdot}14 \pm 0{\cdot}09$

(v) 9 : 10-Dihydroanthracene (0·1M) and 1 : 4-benzoquinone (0·1M) in dioxan at 80°. 2·5 ml. of 0·0970N-Ti^{3+} back-titrated with 0·0407N-Fe^{3+}.

t (min.)	0	8460	11,740	25,000	72,000
x (ml.)	1·27	2·10	2·96	4·02	5·21
10^4k	—	2·5	3·9	5·6	7·0

$10^4k = ca.\ 2{\cdot}5$ (extrapolated)

This extrapolated rate-constant may be too high by a factor of up to 2, depending on the undetermined rate of Diels–Alder addition which is higher than with thymoquinone.

Department of Organic Chemistry,
Imperial College of Science and Technology,
South Kensington, London, S.W.7.

[*Received, February 24th*, 1954.]

Hydrogen Transfer. Part IV. The Use of Quinones of High Potential as Dehydrogenation Reagents.*

By E. A. Braude, A. G. Brook, and R. P. Linstead.

[Reprint Order No. 5155.]

The use of quinones of high potential for the dehydrogenation of hydroaromatic and hydroethylenic systems† has been investigated, tetralin, acenaphthene, and dibenzyl being used as standard donors. Amongst eleven quinones tested, the most effective was 2 : 3-dichloro-5 : 6-dicyano-1 : 4-benzoquinone, followed by tetrachloro-1 : 2-benzoquinone, tetrachloro-1 : 8-diphenoquinone, and tetrachloro-1 : 4-benzoquinone. Dichlorodicyanobenzoquinone converts tetralin into naphthalene in practically quantitative yield at room temperature (5 days) or in boiling benzene solution (2 hr.). Acenaphthene is similarly converted into acenaphthylene (20 hr.), while dibenzyl is partly dehydrogenated to stilbene.

The work described in the two preceding papers has established a definite relation between the oxidation–reduction potentials of quinones and their reactivities in hydrogen-transfer reactions with hydroaromatic compounds. In general, quinones of high potential exhibit high reactivity of this type, although, as would be expected, the precise sequence also shows some dependence on the donor which has not yet been fully elucidated. Chloranil (tetrachloro-1 : 4-benzoquinone), the quinone most frequently employed in the past as a dehydrogenation reagent for preparative purposes (for references, see Part I, *J.*, 1954, 3544),

Transfer-dehydrogenation of hydrocarbons by quinones.
(*In benzene at* 80°, *unless otherwise indicated.*[1])

	Tetralin			Acenaphthene			Dibenzyl		
Acceptor	Time (hr.)	Recovery (%) [a]	Dehydrogn. (%)	Time (hr.)	Recovery (%) [a]	Dehydrogn. (%)	Time (hr.)	Recovery (%) [a]	Dehydrogn. (%)
1 : 4-*Benzoquinones*									
Tetrachloro-	2	80	<10	—	—	—	—	—	—
	20	65	100 [4]	20	55	59 [4]	20	80	<10 [4]
2 : 5-Difluoro- [2]	2	60	13	20	95	17	—	—	—
2 : 5-Dibenzoyl-	2	70	11	20	90	13	—	—	—
2 : 5-Bismethylamino- [3]	2	75	11	20	95	12	—	—	—
2 : 3-Dicyano-	2	50	12	20	40	50	20	85	<10
	2	65	100 [5]	—	—	—	—	—	—
2 : 3-Dichloro-5 : 6-dicyano-	2	70	100	20	65	79	20	50	43
	120	65	76 [6]	120	65	53 [6]	120	80	<10 [6]
1 : 2-*Benzoquinones*									
Tetrachloro-	2	80	100	20	45	60	20	90	12 [4]
Tetrabromo-	2	85	<10	20	30	35	20	85	13 [4]
1 : 8-*Diphenoquinones*									
Unsubstituted	2	60	<10	20	85	<10	20	90	<10
Tetrachloro-	10	80	30	20	35	16	20	80	<10
Tetrabromo-	10	60	18	20	40	26	20	50	<10

[a] Of hydrocarbon. [1] For details of conditions, see Experimental section. [2] This quinone was kindly provided by Dr. G. C. Finger (cf. *J. Amer. Chem. Soc.*, 1951, **73**, 145). [3] As the bistrichloroacetate. [4] In boiling xylene solution (*ca.* 135°). [5] In boiling toluene solution (*ca.* 110°). [6] At room temperature.

has a fairly high potential and is the most reactive yet studied kinetically (Part II), but has generally been used under comparatively drastic conditions, usually above 200°. In many cases, such conditions are probably excessive, but nevertheless it appeared that a systematic investigation of other suitable quinones might afford superior acceptors,

* Part III, preceding paper.

† The term "hydroethylenic" is used with reference to an aliphatic system which is particularly prone to conversion into an ethylenic system; *e.g.*, dehydrogenation of dibenzyl to stilbene.

provided that they combined high potential with reasonable thermal stability and did not undergo alternative reactions with ethylenic and benzenoid compounds.

We chose tetralin, acenaphthene, and dibenzyl as standard donors to represent three types of hydroaromatic and hydroethylenic systems. These were tested against chloranil and ten other quinones under comparable conditions, generally in boiling benzene, toluene, or xylene. The extent of dehydrogenation was determined by isolating the mixture of unchanged and dehydrogenated hydrocarbon chromatographically, and estimating the percentage composition spectrometrically; the ultra-violet absorption bands of naphthalene at 2750 Å, of acenaphthylene at 3230 Å, and of stilbene at 2950 Å proved convenient for this purpose since the hydro-derivatives exhibit only weak absorption at these wavelengths. In most cases, the dehydrogenation product was also identified separately and the extent of transfer was confirmed by isolating the quinol. Details are given in the Experimental section; the main results are collected in the Table.

It may be noted, first, that the relative ease of dehydrogenation of the three donors in the Table is qualitatively independent of the quinone; and comparison with rate measurements on dihydronaphthalenes (Parts II and III, and unpublished work by J. S. Shannon) allows the following sequence to be written :

	1 : 4-Dihydronaphthalene	1 : 2-Dihydronaphthalene	Tetralin	Acenaphthene	Dibenzyl
r (approx.)	1	10^{-2}	10^{-3}	10^{-4}	10^{-5}
ΔE_R (kcal.)	30	25	4	<15	7

This sequence is understandable on the basis of the principles previously discussed. One of the more important factors determining the relative rates (r) will be the stabilisation of the transition state arising from the gain in resonance energy (ΔE_R) accompanying dehydrogenation of the donor. The relevant values, based on the experimental resonance energies (enthalpies) tabulated by Klages (*Ber.*, 1949, **82**, 367; cf. Part III), are shown above; it is assumed that the dehydrogenation of tetralin proceeds in two steps, the formation of 1 : 2-dihydronaphthalene followed by that of naphthalene, and that the first of these is rate-determining. In the three compounds containing a partially hydrogenated six-membered ring, r and ΔE_R decrease in the same order, though by no means proportionally. No thermochemical data are available for the conversion of acenaphthene into acenaphthylene which, in our experiments, takes place distinctly less readily than that of tetralin to naphthalene. [The reverse has been reported by Dost (*Rec. Trav. chim.*, 1952, **71**, 857) for dehydrogenation by chloranil in chlorobenzene. Dost's results are based, however, on determinations of the rate of disappearance of quinone without isolation of products, and this may conceivably be the reason for the discrepancy.] Theory predicts a considerable gain in resonance energy in acenaphthylene (*ca.* 15 kcal.) (cf. Syrkin and Diatkina, *Acta Physicochim. U.R.S.S.*, 1947, **21**, 529; Klement, *Helv. Chim. Acta*, 1949, **32**, 1777; Pullman and Pullman, "Les Théories Electroniques de la Chimie Organique," Masson, Paris, 1952), but this will be partly off-set by an increase in ring-strain in the unsaturated fused five-membered ring. The magnitude of the steric factor is unknown and not readily estimated, but may well be comparable with the quantum-mechanical resonance energy and thus account for the relatively slow dehydrogenation of acenaphthene. Dibenzyl is still less reactive than tetralin or acenaphthene in spite of a larger value of ΔE_R, and an additional factor evidently comes into play when an acyclic ethane unit is undergoing dehydrogenation. Whereas the cyclic systems already possess an approximately uniplanar arrangement in their partly hydrogenated state, the conversion of dibenzyl into stilbene entails a severe loss in freedom of rotation which will result in a decrease in the entropy of activation. A rate factor of 10^2, corresponding to 10 entropy units, arising from this cause is not unreasonable, but the correctness of this interpretation remains to be checked kinetically. Somewhat analogous observations have recently been made by Kooyman (*Discuss. Faraday Soc.*, 1951, **10**, 163; *Rec. Trav. chim.*, 1953, **72**, 330, 342) in regard to homolytic dehydrogenation by trichloromethyl radicals, and discussed in similar terms.

We now turn to the comparison of acceptors. Chloranil (E^0 0·70 v) does not react at a

useful rate with any of the three standard donors at 80°, but causes slow dehydrogenation of tetralin and acenaphthene at 130°. Tetrachloro-1 : 2-benzoquinone (E^0 0·87 v; Conant and Fieser, *J. Amer. Chem. Soc.*, 1924, **46**, 1873) is more effective and dehydrogenates tetralin to naphthalene almost quantitatively within 2 hr. at 80°, but diphenoquinone (E^0 0·95 v; Fieser, *ibid.*, 1930, **52**, 4915) and tetrachloro-1 : 8-diphenoquinone, though they have still higher potentials, are considerably less reactive than tetrachloro-1 : 2-benzoquinone, as are the corresponding bromo-quinones. The reactions of tetralin and dibenzyl with chloranil and with tetrachloro-*o*-benzoquinone have also been investigated in other laboratories (Horner and Merz, *Annalen*, 1950, **570**, 89; Buchta and Kallert, *ibid.*, 1951, **573**, 220; Dost and van Nes, *Rec. Trav. chim.*, 1951, **70**, 403). The results for tetralin are in good agreement with those obtained here, but the results for dibenzyl are not. Dost and van Nes initially reported a 64% conversion of dibenzyl into stilbene with chloranil at 130° (16 hr.), and Dost later revised this figure to 14% (*ibid.*, 1952, **71**, 858); but they gave no details of their analytical procedure. Buchta and Kallert obtained a 23% conversion into stilbene, which was isolated and identified by mixed m. p., under similar conditions (20 hr.). In our hands, repeated experiments yielded no detectable amount (<2%) of stilbene although the total recovery of hydrocarbon was similar (70%) to that (80%) obtained by the German workers. Variations in experimental conditions, such as the exclusion or admission of air or oxygen, had no effect on the result. Moreover, spectroscopic measurements on the reaction mixture showed no measurable decrease in the quinone concentration. It appears that the discrepancy is to be explained either by the initial presence of stilbene in the dibenzyl employed by Buchta and Kallert, or by the existence of some unidentified catalytic influences. Evidence of a reaction consuming quinone was obtained at very high ratios (100 : 1) of hydrocarbon to quinone; this suggests that an impurity in the dibenzyl might be responsible.

Thus, although tetrachloro-1 : 2-benzoquinone exhibits a higher order of reactivity than chloranil, its range of practical application is still rather limited. Since it has been claimed that cholesteryl acetate can be partly converted into the 7-dehydro-derivative by benzoquinone (Milas and Heggie, *J. Amer. Chem. Soc.*, 1938, **60**, 984; Sah, *Rec. Trav. chim.*, 1940, **59**, 454) and that dehydrogenation is promoted by ultra-violet light (Mazza and Migliardi, *Chem. Abs.*, 1943, **37**, 3762), we have examined the use of tetrachloro-1 : 2-benzoquinone for this purpose. The results were entirely negative, however; no spectroscopic evidence for the formation of 7-dehydrocholesteryl acetate was obtained and 85% of the starting material was recovered. The possible effect of illumination was also tested on the reaction between the quinone and 9 : 10-dihydroanthracene which is dehydrogenated at a convenient rate at room temperature, but neither visible nor ultra-violet light had any marked effect under the conditions employed.

Since the completion of the present work, Moore and Waters (*J.*, 1953, 3405) have reported the dehydrogenation of tetralin by chloranil under mercury-arc illumination. Using a large excess of tetralin, they obtained a 50% yield (based on quinone) of 1 : 2-dihydronaphthalene after 39 days and interpreted the reaction as a photochemical one. No control experiments were recorded and as the reaction temperature was not determined comparison with our results is rendered somewhat uncertain. However, the fact that thermal dehydrogenation is complete within less than one day at 130° indicates that illumination had no very large accelerating effect, and quite possibly had none.

Attention was then directed to benzoquinones containing more strongly electron-attracting substituents than chlorine or bromine. Difluoro-, dibenzoyl- and dicyano-1 : 4-benzoquinone (E^0 0·97 v; Rideal, *Trans. Faraday Soc.*, 1925, **21**, 143) all cause slow dehydrogenation of tetralin at 80°, but the improvements in acceptor properties in comparison with chloroanil are not spectacular and the relatively low recoveries of hydrocarbon indicate the occurrence of side reactions, such as the formation of quinol ethers which has been observed by Criegee (*Ber.*, 1936, **69**, 2578). A similar result was obtained with the 2 : 5-bismethylamino-1 : 4-benzoquinone bistrichloroacetate; presumably the concentration of the bisammonium ion, which should have a very high potential, is too small in non-polar solvents to be effective. A striking enhancement in reactivity was observed, however, with 2 : 3-dichloro-5 : 6-dicyano-1 : 4-benzoquinone which was first

described by Thiele and Günther (*Annalen*, 1906, **349**, 59) but has not since been studied. This quinone, the preparation of which has been improved, reacts with tetralin rapidly at 80°, or more slowly at room temperature, to give naphthalene and the quinol in almost quantitative yield. 1 : 4-Dihydronaphthalene is rapidly dehydrogenated at room temperature, and acenaphthene and dibenzyl are dehydrogenated slowly at 80°. Dichlorodicyanoquinone is thus by far the most powerful dehydrogenating agent yet investigated but, although it has proved of great value for thermochemical studies of hydrogen transfer reactions, its wider practical application is unfortunately limited by the incidence of side reactions, particularly at elevated temperatures. Thus, the reaction of the quinone with *cyclo*hexene or ethylbenzene afforded 30—50% yields of the quinol, but no simple dehydrogenation products could be isolated.

Even more powerful dehydrogenator properties might be expected for the unknown tetracyanobenzoquinones and for nitrobenzoquinones. However, attempts to induce reaction between tetrachlorocatechol, tetrachloroquinol, the corresponding diacetates, or chloranil with cuprous cyanide in pyridine gave only intractable products, and attempts to oxidise dinitrocatechol (Kehlmann, *Helv. Chim. Acta*, 1923, **6**, 952) and dinitroquinol (Nietzki and Noll, *Ber.*, 1893, **26**, 2183) to the corresponding quinones were also unsuccessful.

Experimental

Materials.—Chloranil was a recrystallised commercial sample, m. p. 290°. 2 : 5-Difluorobenzo-1 : 4-quinone was kindly provided by Dr. G. C. Finger (cf. *J. Amer. Chem. Soc.*, 1951, **73**, 145). 2 : 5-Dibenzoylbenzoquinone, prepared according to Bogart and Howells (*ibid.*, 1930, **52**, 837), formed orange needles, m. p. 163—164°. 2 : 5-Bismethylaminobenzoquinone, prepared according to Mylius (*Ber.*, 1885, **18**, 467), formed red needles, m. p. 173—174°; its bistrichloroacetate, m. p. 111—113°, was precipitated when a warm solution of the quinone (1 mol.) and trichloroacetic acid (2 mols.) in benzene was cooled. 2 : 3-Dicyano-, m. p. 176°, and 2 : 3-dicyano-5 : 6-dichloro-benzoquinone, m. p. 202°, were prepared according to Thiele (*Ber.*, 1900, **33**, 675; *Annalen*, 1906, **349**, 45; Helferich, *Ber.*, 1921, **54**, 155; 1923, **56**, 1112) but oxidation of the quinols was carried out by a modified procedure (Brook *J.*, 1952, 5040) which greatly accelerated the reaction and improved the yield. The finely ground dicyano-quinol (20 g.) was suspended in carbon tetrachloride (300 ml.), and nitrogen oxides (6 g., prepared by adding 100 g. of arsenious oxide to a cooled mixture of 83 ml. of fuming nitric acid and 33 ml. of concentrated sulphuric acid, warming gently if necessary to initiate reaction, and condensing the red-brown fumes by means of a water-condenser and ice-cooled receiver) were added during 10 min. with vigorous stirring. The carbon tetrachloride layer became initially blue and finally yellow. Stirring was continued for a few minutes, and the suspension was then filtered. The solid product was washed with carbon tetrachloride and crystallised from chloroform–benzene, giving the quinone (18 g., 90%). By this method, the 5-step preparation of dichlorodicyanoquinone from quinol can be carried out in 2 days with an overall yield of 70%. Tetrachlorobenzo-1 : 2-quinone, m. p. 131—132°, and tetrabromobenzo-1 : 2-quinone, m. p. 148—150°, were prepared according to Jackson and Koch (*Amer. Chem. J.*, 1908, **39**, 83, 497). 1 : 8-Diphenoquinone was obtained from 4 : 4′-dihydroxydiphenyl (Willstätter and Kalb, *Ber.*, 1905, **38**, 1232) by oxidation with active lead dioxide in boiling benzene–dioxan (5 : 1) (Kuhn and Hammer, *Chem. Ber.*, 1950, **83**, 413) or, more conveniently, by shaking an ethereal solution with a solution of ceric ammonium sulphate in dilute sulphuric acid. The quinone was precipitated and, after one crystallisation from boiling benzene in the presence of charcoal, had m. p. 165° (decomp.). Tetrachloro- and tetrabromo-diphenoquinone were prepared according to Magatti (*Ber.*, 1880, **13**, 224).

Tetralin, purified by refluxing with sodium in nitrogen and fractionation, had b. p. 207—208°, n_D^{20} 1·5463. Acenaphthene was recrystallised from ethanol and had m. p. 96°. Dibenzyl was recrystallised from ethanol and had m. p. 52°. Benzene, toluene, xylene, and tetrahydrofuran were purified by refluxing with sodium and distillation.

Dehydrogenations. General Procedure.—Solutions, approx. 1M with respect to donor and 1·05M with respect to the quinone, were heated under reflux, generally in nitrogen. All the solutions were initially homogeneous at the b. p. At the end of the appropriate period (see Table), the reaction mixture was diluted with about five volumes of light petroleum (b. p. 40—60°) and the precipitate of quinol and unchanged quinone was filtered off and extracted with boiling light petroleum. The combined petroleum solutions were passed through a short (8″ × ½″) alumina column, and the column was washed with additional petroleum until no more

hydrocarbon could be eluted. The petroleum eluates were dried and evaporated, and the residue was weighed, giving the total hydrocarbon recovery (see Table). In a few cases, the hydrocarbon was isolated by steam-distillation instead of by extraction with petroleum. The extent of dehydrogenation in the recovered hydrocarbon was determined spectrometrically in ethanol solution, using the maxima at 2750 Å ($E^{1\%}_{1\,cm.}$ 440) for naphthalene, at 3230 Å ($E^{1\%}_{1\,cm.}$ 650) for acenaphthylene, and at 2950 Å ($E^{1\%}_{1\,cm.}$ 1500) for stilbene. Tetralin, acenaphthene, and dibenzyl have $E^{1\%}_{1\,cm.}$ <10, 90, and <10, respectively, at the corresponding wave-lengths. Some typical experiments are recorded in detail below.

Dibenzyl and Chloranil (with J. S. Shannon).—(*a*) Dibenzyl (1·8 g.), chloranil (2·7 g.), and xylene (11 ml.) were refluxed for 20 hr. under nitrogen. The solution was diluted with light petroleum, filtered, passed through alumina, and evaporated, giving only unchanged dibenzyl (1·3 g., 70%), m. p. 52°, $E^{1\%}_{1\,cm.}$ at 2940 Å <10.

(*b*) The above experiment was repeated, but with access of air during the refluxing period, to simulate the conditions employed by Dost and van Nes (*Rec. Trav. chim.*, 1951, **70**, 403). The result was the same as in (*a*). In a further experiment, a slow stream of air was passed through the solution : only unchanged dibenzyl (70%) was again obtained.

(*c*) Dibenzyl (6 g.), chloranil (13 g.), and xylene (60 ml.) were heated under reflux for 24 hr. The solution was cooled, filtered, washed with alkaline sodium dithionite (hydrosulphite) and water, dried ($CaCl_2$), and distilled at atmospheric pressure through a 6″ column to remove most of the xylene. The remaining liquid was distilled under reduced pressure through a 6″ Steadman column. Four fractions (total 4·2 g., 70%) were collected all of which solidified on cooling and then had m. p. 53°. The first three fractions all had b. p. 148°/12 mm., $E^{1\%}_{1\,cm.}$ <10 at 2950 Å. The fourth fraction (0·9 g.) had b. p. 150—160°/12 mm., $E^{1\%}_{1\,cm.}$ 60 at 2950 Å. This corresponds to a maximum stilbene content of 4% in this fraction, and of 1% in the total product. For apparently identical conditions, Buchta and Kallert (*Annalen*, 1951, **573**, 220) reported a 23% yield of stilbene.

(*d*) In an attempt to throw some light on the discrepant results with this system, a number of experiments were carried out in which any disappearance of choranil rather than appearance of stilbene was sought by spectrometric measurements in the visible range. Solutions of chloranil in xylene or phenetole exhibit $E^{1\%}_{1\,cm.}$ 35·5 at 4400 Å and 0·285 at 5700 Å, and are stable for 24 hr. at 135°. With 0·1M-choranil, no significant change was detectable during 6 hr. in the presence of 0·1M- or 1M-dibenzyl. However, a phenetole solution 0·02M with respect to chloranil and 1M with respect to dibenzyl shows a rapid decrease in chloranil, $E^{1\%}_{1\,cm.}$ at 4400 Å falling from 35·5 to 2·6 in 3 hr. These results indicate that disappearance of chloranil under such conditions is due to reaction with an unidentified impurity in the dibenzyl.

Tetralin and Tetrachloro-1 : 2-benzoquinone.—Tetralin (1·3 g.), the quinone (5·0 g.), and benzene (15 ml.) were refluxed for 2 hr. in nitrogen. The solution was steam-distilled and the distillate extracted with ether. The ether solution was dried and evaporated, giving naphthalene (1·0 g., 78%), m. p. and mixed m. p. 80°. The non-volatile residue from the distillation was recrystallised from acetic acid, and then from aqueous ethanol, giving tetrachlorocatechol (3·0 g., 60%), m. p. and mixed m. p. 193°.

Dibenzyl and Tetrachloro-1 : 2-benzoquinone.—Dibenzyl (1·8 g.), the quinone (2·2 g.), and xylene (10 ml.) were refluxed for 20 hr., during which some hydrogen chloride was evolved. The solution was diluted with light petroleum (50 ml.), chromatographed, and evaporated, giving a colourless solid product (1·6 g.), m. p. 44—62°. A solution in ethanol showed $\lambda_{max.}$ 2950 Å, $E^{1\%}_{1\,cm.}$ 175, corresponding to a stilbene content of 12%.

Tetralin and Dichlorodicyanoquinone.—Tetralin (0·65 g.), the quinone (1·14 g.), and benzene (5 ml.) were refluxed for 45 min., during which the initially red solution became colourless. More quinone (1·14 g.) in benzene (2 ml.) was added and the solution was refluxed for a further 75 min. After dilution with light petroleum, the solution was filtered, passed through alumina, and evaporated, giving naphthalene (0·42 g., 70%), m. p. and mixed m. p. 79—80°. The petroleum-insoluble residue was crystallised from aqueous ethanol, giving colourless dichlorodicyanoquinol (0·7 g., 61%), decomp. 263°.

Acenaphthene and Dichlorodicyanoquinone.—Acenaphthene (0·38 g.), the quinone (0·57 g.), and benzene (5 ml.) were refluxed for 20 hr., a white precipitate being formed. The mixture was diluted with light petroleum, filtered, passed through alumina, and evaporated, giving a bright yellow solid (0·25 g., 66%), m. p. 91—94°. A solution in ethanol showed $\lambda_{max.}$ 3240 Å, $E^{1\%}_{1\,cm.}$ 535, corresponding to an acenaphthylene content of 79%. Two crystallisations from ethanol raised the m. p. to 94—95°, undepressed on admixture with pure acenaphthylene.

Dibenzyl and Dichlorodicyanoquinone.—Dibenzyl (1·27 g.), the quinone (1·68 g.) and benzene

(7 ml.) were refluxed for 20 hr. in nitrogen. The solution was diluted with light petroleum (40 ml.) passed through alumina which was washed with additional solvent (150 ml.), and evaporated, giving a colourless, solid product (0·61 g., 50%), m. p. 62—104°. A solution in ethanol exhibited $\lambda_{max.}$ 2950 Å, $E^{1\%}_{1\,cm.}$ 650, corresponding to a stilbene content of 43%. After several crystallisations from ethanol, the m. p. was raised to 123°, undepressed on admixture with pure *trans*-stilbene.

Grateful acknowledgment is made to the Nuffield Foundation for a Fellowship (A. G. B.). We thank Dr. L. M. Jackman and Mr. J. S. Shannon for assistance.

Department of Organic Chemistry,
Imperial College of Science and Technology,
South Kensington, London, S.W.7.

[*Received, February 24th,* 1954.]

Hydrogen Transfer. Part V. Dehydrogenation Reactions with Diphenylpicrylhydrazyl.*

By E. A. Braude, A. G. Brook, and R. P. Linstead.

[Reprint Order No. 5156.]

Homolytic hydrogen transfer between various donors and the " stable " free radical, diphenylpicrylhydrazyl, has been investigated. Hydroaromatic donors such as the dihydrobenzenes react rapidly at 60—100°; the sequence of reactivity is the same as in heterolytic dehydrogenation by quinones (*e.g.*, 1 : 4-dihydronaphthalene > 9 : 10-dihydroanthracene > 1 : 2-dihydronaphthalene > acenaphthene) but the energies of activation are rather larger.

Dibenzyl does not react appreciably with diphenylpicrylhydrazyl at 80°, whereas benzylaniline is readily dehydrogenated to benzylideneaniline and hydrazobenzene is converted into azobenzene almost instantaneously at room temperature. The radical can also be " titrated " with diethyl 1 : 4-dihydrolutidine-3 : 5-dicarboxylate. It is suggested that the very pronounced and quite generally encountered difference in reactivity between donors containing C–H and N–H bonds has a stereochemical cause and is due to the fact that nitrogen passes much more readily than carbon from a tetrahedral to a planar, trigonal configuration.

Whereas numerous reactions are known involving the abstraction of hydrogen atoms, particularly from C–H, N–H, and O–H bonds, by free radicals of short life (cf. Waters, " The Chemistry of Free Radicals, Oxford Univ. Press, 1946; Steacie, " Atom and Free Radical Reactions," Reinhold Publ. Corp., New York, 1946; Trotman-Dickinson, *Quart. Reviews*, 1953, **7**, 198; Kooyman and Strang, *Rec. Trav. chim.*, 1953, **72**, 330, 342), very few cases have been described of homolytic hydrogen transfer to " stable " free radicals. Although stable radicals will be intrinsically less reactive hydrogen acceptors than are " unstable " radicals, in practice the difference will be considerably reduced by the very much higher concentrations of stable radicals which are attainable. For quantitative investigations, stable radicals have the additional advantage that their concentrations are readily and directly measurable.

For a preliminary study, we chose diphenylpicrylhydrazyl (Goldschmidt and Renn, *Ber.*, 1922, **55**, 628) which has been shown by magnetic measurements to exist mainly as the monomeric radical both in the solid state and in solution (Müller, Müller-Rodloff, and Bunge, *Annalen*, 1935, **520**, 235; Allen and Sugden, *J.*, 1936, 440), although the quantitative significance of the data is rendered somewhat uncertain by the unknown diamagnetic contribution (Selwood and Dobres, *J. Amer. Chem. Soc.*, 1950, **72**, 3860). The strong hydrogen-acceptor properties of diphenylpicrylhydrazyl are indicated by the instantaneous conversion of quinol into benzoquinone (Goldschmidt and Renn, *loc. cit.*), a reaction also exhibited by other stable free radicals, such as triphenylmethyl (Goldschmidt and Wurzschmitt, *Ber.*, 1922, **55**, 3217). Diphenylpicrylhydrazyl similarly dehydrogenates tetrachloro-

* Part IV, preceding paper.

quinol, tetrachlorocatechol, and tetrachloro-4 : 4'-dihydroxydiphenyl to the corresponding quinones; with the first two, as with quinol, the reaction is instantaneous under the conditions used (in chloroform solution at room temperature), but with the diphenyl derivative a just perceptible reaction period of a few seconds can be observed. This accords with the fact that the diphenoquinone has the highest oxidation–reduction potential (*ca.* 1·0 v; Part IV) and leads to the deduction that the " potential " of the diphenylpicrylhydrazyl–diphenylpicrylhydrazine system is of the order of 1·2 v, intermediate between those of diphenoquinone and of quadrivalent lead (1·7 v) which is used in the preparative oxidation of the hydrazine.

The main results of experiments on hydrogen transfer between diphenylpicrylhydrazyl and hydroaromatic donors are shown in Table 1. The two dihydrobenzenes, 1 : 2- and 1 : 4-dihydronaphthalene, and 9 : 10-dihydroanthracene all react fairly rapidly in boiling chloroform or carbon tetrachloride solution, giving the hydrazine and benzene, naphthalene, or anthracene in almost quantitative yields. Under similar conditions, little or no reaction is observed with tetralin, acenaphthene, 9 : 10-dihydrophenanthrene, or dibenzyl, although some dehydrogenation is observed with acenaphthene at higher temperatures.

TABLE 1. *Dehydrogenations with diphenylpicrylhydrazyl.*

Donor	Solvent *	Time (hr.)	Total yield (%)	Dehydrogn. (%)
1 : 2-Dihydrobenzene	CCl_4	3	—	>50
1 : 4-Dihydrobenzene	,,	1	—	>50
1 : 2-Dihydronaphthalene	,,	5	68	100
1 : 4-Dihydronaphthalene	$CHCl_3$	1	74	100
9 : 10-Dihydroanthracene	CCl_4	3	56	95
Tetralin	$CHCl_3$	3	73	<10
Acenaphthene	C_6H_6	16	50	18
9 : 10-Dihydrophenanthrene	$CHCl_3$	20	40	<10
Dibenzyl	,,	24	76	< 2
Benzylaniline	,, †	6	90	100
Hydrazobenzene	,, ‡	0·2	96	100
Diethyl 1 : 4-dihydrolutidine-3 : 5-dicarboxylate	,, ‡	0·2	95	100

* At the b. p. of *ca.* 1M-solutions with respect to donor and hydrazyl, except where otherwise stated. For details, see experimental section. † At 40°. ‡ At 20°.

A preliminary kinetic investigation of some of the above reactions in dioxan was carried out by following the rate of disappearance of the hydrazyl spectrometrically. The results are of a low order of accuracy owing to several complicating factors, particularly the thermal instability of the hydrazyl solution under the conditions employed, but suffice to show that the reactions obey approximately the third-order rate law, $v = k_3[\text{donor}][\text{hydrazyl}]^2$, as expected from the equation :

$$XH_2 + 2R_2N{\cdot}\dot{N}R' \longrightarrow X + 2R_2N{\cdot}NHR'$$

As with other homogeneous, third-order processes, the reaction almost certainly involves a fast, reversible association of two of the reacting species followed by a rate-determining attack on this intermediate by the third component. The initial association could occur either (1) between two hydrazyl radicals to form the tetrazan, or (2) between a tetrazyl radical and the hydrocarbon to form a molecular complex. Although we cannot yet distinguish between these two possibilities, the second appears the more probable, particularly since complex formation will be assisted by the picryl group.

$$(1)\quad 2R_2N{\cdot}\dot{N}R' \underset{\text{Fast}}{\rightleftharpoons} R_2N{\cdot}NR'{\cdot}NR'{\cdot}NR_2 \xrightarrow[\text{Slow}]{XH_2} 2R_2N{\cdot}NHR' + X$$

$$(2)\quad R_2N{\cdot}\dot{N}R' + XH_2 \underset{\text{Fast}}{\rightleftharpoons} R_2N{\cdot}\dot{N}R'{\cdot}XH_2 \xrightarrow[\text{Slow}]{R_2N{\cdot}\dot{N}R'} 2R_2N{\cdot}NHR' + X$$

Rate constants and energies of activation for three of the donors are given in Table 2. The first point of interest is the sequence of donor reactivity :

1 : 4-Dihydronaphthalene>9 : 10-Dihydroanthracene>1 : 2-Dihydronaphthalene

which is the same as that found in hydrogen transfer to quinone acceptors (Part III). This parallelism is not unexpected, since the relative rates will be governed by the same factor—the stabilisation of the transition state arising from the gain in resonance energy accompanying dehydrogenation—independently of whether the C–H bond fission is heterolytic or homolytic. A second point of interest is the magnitude of the energies of activation, which are considerably higher than those found in the dehydrogenation of quinones (cf. Part III). Thus, whereas the reaction of 1 : 4-dihydronaphthalene with diphenylpicrylhydrazyl has $E_A = 26$ kcal./mole, the corresponding reaction with tetrachloro-1 : 2-benzoquinone which proceeds with comparable rates under similar conditions has $E_A = 13$ kcal./mole (unpublished work by J. S. Shannon). This difference will be partly due to the fact that the observed E_A for the radical reaction includes the enthalpy change of the pre-equilibrium, but this is unlikely to amount to as much as 13 kcal./mole. It is probable that the high value of E_A for the radical reaction is predominantly due to the fact that in hydrogen transfer to the radical there is a gain in resonance energy in the donor but a loss of resonance energy in the acceptor, whereas in hydrogen transfer to the quinone there is a gain in resonance energy in both donor and acceptor, and consequently a greater stabilisation of the transition state. A third point of interest is the fairly large positive value of the entropy of activation which is typical of free-radical reactions, though the observed value will again include any entropy change accompanying the postulated pre-equilibrium.

TABLE 2. *Extrapolated third-order rate constants* (k_3, l.^{2} mole^{-2} min.$^{-1}$), *energies of activation* (E_A, kcal./mole), *and entropies of activation* (ΔS, e.u.) *for the reaction between hydrocarbons and diphenylpicrylhydrazyl in dioxan.*

Hydrocarbon	t	k_3	E_A	$\Delta S_{80°}$
1 : 4-Dihydronaphthalene	56°	0·8	26	12
	80	12		
1 : 2-Dihydronaphthalene	56	0·04	33	27
	80	1·2		
9 : 10-Dihydroanthracene	56	0·1	29	14
	80	2·0		

In marked contrast to dibenzyl, its aza-analogue, benzylaniline, reacts even at 40° to give benzylideneaniline, while the diaza-analogue, hydrazobenzene, is rapidly converted into azobenzene at room temperature. The much greater ease of dehydrogenation of systems containing N–H in place of C–H bonds is also illustrated by diethyl 1 : 4-dihydrolutidine-3 : 5-dicarboxylate which is dehydrogenated almost instantaneously and can be "titrated" with diphenylpicrylhydrazyl at room temperature in chloroform. The high reactivity of N–H bonds in hydrogen transfer appears to be a general phenomenon, which is reflected in the prominent part played by nitrogen-containing heterocycles in biological systems (cf. Waters, *op. cit.*, Chap. XII), and deserves some comment. The bond energies and bond dissociation energies of C–H and N–H, as well as the resonance energies of unsaturated systems containing C=C or C=N, are very similar (cf. Szwarc, *Chem. Reviews*, 1950, **47**, 75; Wheland, "The Theory of Resonance," Wiley, New York, 1944), so that such thermodynamic differences cannot be responsible for the difference in reactivity. The explanation is most probably to be sought in the much greater ease with which nitrogen can pass from the tetrahedral to a planar configuration, as is indicated by, *inter alia*, the failure to resolve compounds of tervalent nitrogen (for summaries, see Shriner, Adams, and Fuson in Gilman, "Organic Chemistry," Wiley, New York, 1943, p. 402; Maitland, *Ann. Reports*, 1939, **36**, 239), except in one case where inversion is structurally precluded (Prelog and Wieland, *Helv. Chim. Acta*, 1944, **27**, 1127), and by spectroscopic evidence (cf. Herzberg, "Infra-red and Raman Spectra," Van Nostrand, New York, 1945; Walsh, *J.*, 1953, 2296). At a carbon atom, planarity will therefore be established only concurrently with the fission of the C–H bond and any resonance stabilisation of the resulting intermediate will become effective only at a fairly advanced stage of the dehydrogenation. At a nitrogen atom, on the other hand, planarity can be established even in the tercovalent state at the expense of a relatively small amount of energy (*ca.* 10 kcal.; Maitland, *loc. cit.*), and fission of the N–H bond will be assisted by resonance stabilisation well before the transition

state is reached, with a consequent lowering of the energy of activation. This difference between the reactivity of C–H and N–H bonds should exist independently of whether the hydrogen is removed heterolytically as a hydride anion (as postulated in dehydrogenation by quinones) or homolytically as a hydrogen atom (as in dehydrogenation by free radicals); in either case the resulting intermediate cation or radical will adopt a planar configuration at the carbon or nitrogen atom concerned and be stabilised by charge resonance or electron resonance.

Experimental

Dehydrogenations.—The preparative experiments were carried out as described in the preceding paper. *NN*-Diphenylpicrylhydrazyl, m. p. 137—138°, was prepared according to Goldschmidt and Renn (*Ber.*, 1922, **55**, 628; cf. *Annalen*, 1924, **437**, 194) except that in the final stage, 2 parts by weight of specially reactive lead dioxide obtained by hydrolysis of lead tetra-acetate (Kuhn and Hammer, *Ber.*, 1950, **83**, 413) were employed, instead of 15 parts by weight of ordinary lead dioxide. Solutions approx. 1M with respect to the hydrazyl and the donor were refluxed under dry nitrogen for the appropriate time (see Table 1). During the reactions, the colour changed from deep violet to red and finally pale orange. The solutions were then diluted with 10 volumes of light petroleum (b. p. 40—60°) which resulted in almost quantitative precipitation of crystalline diphenylpicrylhydrazine (smaller volumes of petroleum tend to give a gummy precipitate). After filtration, the solutions were passed through a short column of alumina, the product was eluted with more solvent and the eluates were evaporated. With the *cyclo*hexadienes, the procedure was modified by directly distilling the reaction mixture and estimating benzene spectrometrically in the distillate. Details of some typical experiments are given below.

(*a*) 1 : 4-Dihydronaphthalene (0·26 g.), hydrazyl (3·94 g.), and chloroform (5 ml.) were refluxed for 1 hr. Light petroleum (50 ml.) was added and the hydrazine (3·2 g.), m. p. 163—165°, was filtered off. The solution was passed through alumina and evaporated, giving naphthalene (0·19 g., 74%), m. p. and mixed m. p. 80°.

(*b*) Acenaphthene (0·49 g.), hydrazyl (2·55 g.), and benzene (7 ml.) were refluxed for 16 hr. Working up as under (*a*) gave 0·24 g. (50%) of recovered hydrocarbon, m. p. 78—82°. It showed $E^{1\%}_{1\,cm.}$ 115 at 3230 Å, corresponding to an acenaphthylene content of 18%.

(*c*) Hydrazobenzene (0·2 g.) in chloroform (3 ml.) was added to the hydrazyl (0·84 g.) in chloroform (3 ml.). The colour of the radical immediately disappeared. On adding light petroleum, diphenylpicrylhydrazine (0·79 g., 94%), m. p. 165°, was precipitated. The solution was passed through alumina and evaporated, giving azobenzene (0·2 g.), m. p. and mixed m. p. 68°.

(*d*) A solution of diethyl 1 : 4-dihydrolutidine-3 : 5-dicarboxylate (1·7 g.) and hydrazyl (5·0 g.) in chloroform (25 ml.) was kept for 10 min. at 30° and then diluted with light petroleum (200 ml.). The bright red precipitate of diphenylpicrylhydrazine (4·9 g.) was filtered off and had m. p. 167—168° after one crystallisation from ethanol–chloroform. The petroleum solution was evaporated, leaving an almost colourless residue (1·7 g.) which was dissolved in light petroleum (b. p. 100—120°), poured on alumina, and eluted with benzene–chloroform (1 : 1), giving pure diethyl lutidine-3 : 5-dicarboxylate (1·3 g.), m. p. 73—74°.

Rate Measurements.—These were carried out in reaction vessels of the type described by Braude, Jones, and Stern (*J.*, 1946, 396), but of only 10-ml. capacity. 5 Ml. of approx. 0·2M-solution of the hydrazyl were placed in the flask and, after thermal equilibrium was attained, a 0·1-ml. sample was withdrawn by means of a specially constructed long-stem pipette and dissolved in 25 ml. of carbon tetrachloride. The pipette was pre-warmed to the reaction temperature by keeping it in a jacketed pistol surrounded by boiling acetone or benzene. As soon as possible after the removal of the initial sample, the weighed amount of hydrocarbon to give a 0·5M-solution was dropped into the flask in a small capsule, and the vessel was vigorously shaken. Further samples were then taken at appropriate intervals.

The sample solutions were then diluted further with solvent (2 in 25 ml.), and the hydrazyl concentration was determined spectrometrically by means of a Unicam SP 500 instrument and a 1-cm. cell; extinction was measured at 5180 Å where the hydrazyl exhibits a maximum with ε 12000. [For chloroform solutions, Goldschmidt and Graef (*Ber.*, 1928, **61**, 1858) give $\lambda_{max.}$ 5300 Å, ε 6500, while Poirier, Kahler, and Benington (*J. Org. Chem.*, 1952, **17**, 1437) give $\lambda_{max.}$ 5300 Å, ε 14,500.] It was established that Beer's law is obeyed at the maximum in the range 0·1—1·5 *E*, and is little affected by the presence of diphenylpicrylhydrazine which has ε *ca.* 500 at 5180 Å.

The third-order rate constants were calculated from the standard equation:

$$k_3 = (1/t)(a - 2b)^2[2x(2b - a)/a(a - 2x) + \ln b(a - 2x)/a(b - x)]$$

where t = time (min.), a = initial concentration of hydrazyl (mole/l.), b = initial concentration of hydrocarbon, and $2x$ = change in hydrazyl concentration at t. Details of two typical runs are given below.

(i) Hydrazyl and dihydroanthracene (0·450 g.; 0·5M) in dioxan (5 ml.) at 56°. Samples diluted 2 : 625.

t	0	7	15	35	60	120	360
E (5180 Å)	0·739	0·643	0·573	0·457	0·358	0·214	0·037
a (calc.)	0·190	0·165	0·147	0·118	0·092	0·055	—
k_3	—	0·114	0·104	0·097	0·097	0·119	—

(ii) Reagents as above, at 80°.

t	0	2	6	10	28	90
E (5180 Å)	0·557	0·355	0·244	0·149	0·103	0·035
a (calc.)	0·144	0·092	0·058	0·039	0·027	—
k_3	—	2·02	1·81	2·02	1·86	—

Grateful acknowledgment is made to the Nuffield Foundation for a Fellowship (A. G. B.).

Department of Organic Chemistry,
Imperial College of Science and Technology,
South Kensington, London, S.W.7.

[*Received, February 24th,* 1954.]

Hydrogen Transfer. Part VI. Metal-catalysed Transfer-hydrogenation of Ethylenic Compounds.*

By E. A. Braude, R. P. Linstead, and P. W. D. Mitchell.

[Reprint Order No. 5157.]

*cyclo*Hexene, and similar hydroaromatic compounds which readily disproportionate at moderate temperatures in the presence of metal catalysts, can be used as hydrogen donors for the reduction of ethylenic and acetylenic bonds in hydrocarbons and carboxylic acids. Thus, stilbene is quantitatively converted into dibenzyl, and maleic acid into succinic acid, on treatment with *cyclo*hexene and palladium in boiling tetrahydrofuran at 65°. The disproportionation of the donors is suppressed by the acceptors to varying extents; in favourable cases, transfer occurs exclusively although it usually proceeds more slowly than does disproportionation in the absence of acceptor. The results can be interpreted in terms of co-adsorption of the donor and acceptor on the catalyst surface.

The first investigation of metal-catalysed hydrogen-transfer under mild conditions was described by Wieland in a classical paper published just over forty years ago (*Ber.*, 1912, **45**, 484). Wieland showed, *inter alia*, that dihydronaphthalene disproportionates rapidly in the presence of colloidal palladium at room temperature to naphthalene and tetralin, and he predicted that dihydrobenzene would undergo an analogous reaction even more readily. This was later confirmed by Zelinski and Pavlov (*Ber.*, 1933, **66**, 1420) who found, moreover, that *cyclo*hexene also disproportionates with ease in the presence of palladium to give *cyclo*hexane and benzene (cf. Corson and Ipatieff, *J. Amer. Chem. Soc.*, 1939, **61**, 1056). By contrast, 9 : 10-dihydroanthracene, the disproportionation of which would involve the loss of benzenoid character in one ring, only undergoes a small amount of dehydrogenation under similar conditions.

Wieland employed equimolar or even larger proportions of palladium in his experiments; he considered the metal to be a reactant rather than a catalyst and represented disproportionation by two distinct steps, dehydrogenation of one molecule with the formation of

* Part V, preceding paper.

chemisorbed hydrogen, followed by hydrogenation of another molecule. An alternative view is that disproportionation at moderate temperatures is a linked process in which dehydrogenation and hydrogenation take place simultaneously at the catalyst surface, *i.e.*, that disproportionation involves direct hydrogen transfer between identical donors and acceptors. The latter view receives support if the reaction proceeds stoicheiometrically even under conditions favouring the removal of any chemisorbed hydrogen, *e.g.*, when small proportions of metal are used in a boiling solvent. Such is found to be the case in the disproportionation of *cyclo*hexene in tetrahydrofuran, and further evidence on this point is given below. The disproportionation of other hydrobenzenoid compounds under similar conditions normally appears to follow the same course (Linstead, Braude, Mitchell, Wooldridge, and Jackman, *Nature*, 1952, **169**, 100); evolution of hydrogen is observed only at elevated temperatures at which dehydrogenation also takes place with systems which do not disproportionate (cf. Knoevenagel and Bergdolt, *Ber.*, 1903, **36**, 2857; Linstead and his co-workers, *J.*, 1937, 1146; 1940, 1127, 1134, 1139). The postulate of "linked disproportionation" does not exclude the presence of some chemisorbed hydrogen on the catalyst; in fact, unpublished experiments by Dr. K. R. H. Wooldridge and Mr. K. D. E. Whiting on the kinetics of disproportionation of *cyclo*hexene under such conditions have shown that the reaction is accelerated by absorbed hydrogen. Apart from its possible effects on the surface dimensions, the main function of chemisorbed hydrogen may indeed be to act as a link between adsorbed but non-adjacent *cyclo*hexene molecules and to reduce the degree of close approach required for the reaction (Figs. 1 and 2).*

FIG. 1. *Schematic representation of termolecular disproportionation of* cyclo*hexene.*

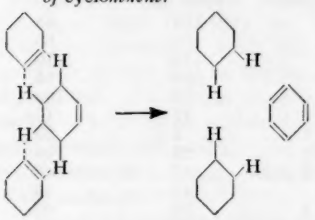
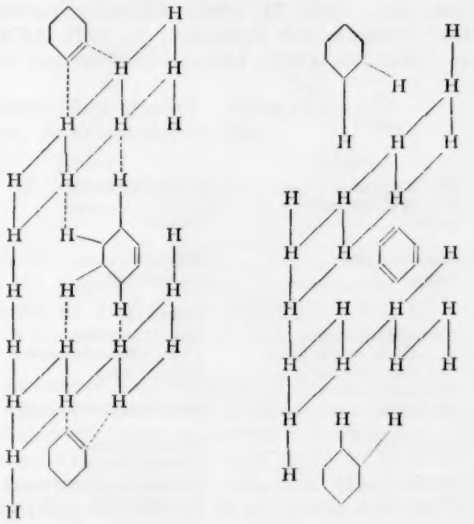


FIG. 2. *Schematic representation of termolecular disproportionation of* cyclo*hexene in presence of chemisorbed hydrogen.*



Another question which arises in the case of *cyclo*hexene is whether disproportionation is bimolecular or termolecular, *i.e.*, whether *cyclo*hexadiene is an intermediate in the formation of benzene or whether four hydrogen atoms are removed simultaneously. Kinetically, there is no objection to a termolecular reaction on a catalyst surface, while energetically it will be favoured owing to the much larger resonance energy of benzene compared with that of *cyclo*hexadiene. The facts that no spectroscopically detectable amount of *cyclo*hexa-1 : 3-diene is formed during the disproportionation of *cyclo*hexene, and that *cyclo*-

* Figures 1, 2, and 3 are only intended to illustrate the topography of the surface reaction, and no account has been taken of the (unknown) conformation of the *cyclo*hexene ring on the catalyst. The stereochemical aspects will be discussed in a later paper, in conjunction with kinetic data.

pentene, *cyclo*heptene, and *cyclo*octene are not disproportionated under similar conditions, are in accord with (though of course they do not prove) the termolecular mechanism for *cyclo*hexene. The simultaneous, rather than stepwise, removal of six hydrogen atoms in the dehydrogenation of *cyclo*hexane has been favoured for similar reasons (Taylor, *J. Amer. Chem. Soc.*, 1938, **60**, 627).

The possibility thus suggests itself of effecting hydrogen transfer between non-identical donors and acceptors without the intervention of molecular hydrogen. Such processes are almost unknown in the field of heterogeneous liquid–solid phase reactions, although they are thought to be of great importance in biological systems. Use has occasionally been made of donors such as tetralin (Akabori and Suzuki, *Proc. Imp. Acad. Japan*, 1929, **5**, 255; Suzuki and Inove, *ibid.*, 1930, **6**, 266; Kinder and Peschke, *Annalen*, 1932, **497**, 193; Orchin, *J. Amer. Chem. Soc.*, 1944, **66**, 535; Ashida, *J. Agric. Chem. Soc. Japan*, 1944, **20**, 621; 1950, **23**, 2311), and *cyclo*hexanol and other alcohols (Armstrong and Hilditch, *Proc. Roy. Soc.*, 1919, *A*, **96**, 322; Belopolski and Maksimov, *Bull. Far East Branch Acad. Sci. U.S.S.R.*, 1936, **17**, 3; *Chem. Abs.*, 1936, **30**, 5939; *Maslovoino Zhirovoe Delo*, 1937, **13**, 13; *Chem. Abs.*, 1937, **31**, 7397; Rush and Dvinyaninkova, *J. Appl. Chem. U.S.S.R.*, 1937, **10**, 702; Puzanov, *ibid.*, 1938, **11**, 670; Dubois, *Compt. rend.*, 1947, **224**, 1234; Kleiderer and Kornfeld, *J. Org. Chem.*, 1948, **13**, 455; Mechelen, *Bull. Soc. chim. Belg.*, 1949, **58**, 247; Akabori and Sataki, *J. Chem. Soc. Japan*, 1949, **70**, 84; Pietra and Traverso, *Gazzetta*, 1951, **81**, 687), for the reduction of various acceptors in the presence of nickel or palladium; and conversely acceptors such as maleic and cinnamic acid (Akabori and Saito, *Proc. Imp. Acad. Japan*, 1930, **6**, 236; *Ber.*, 1930, **63**, 2245; Majima and Marahasi, *Proc. Imp. Acad. Tokyo*, 1934, **10**, 341; Hoshino and Takivra, *Bull. Soc. Chem. Japan*, 1936, **11**, 218; Kotake and Kubota, *Annalen*, 1940, **544**, 253; Elderfield and Maggiolo, *J. Amer. Chem. Soc.*, 1949, **71**, 1906; Culvenor, Goldsworthy, Kirby, and Robinson, *J.*, 1950, 1485; Badcock and Pausacker, *J.*, 1951, 1373; Doering and Rhoads, *J. Amer. Chem. Soc.*, 1953, **75**, 4738), benzene (Adkins and his co-workers, *ibid.*, 1948, **70**, 381; 1949, **71**, 2955; Pines, Olberg and Ipatieff, *ibid.*, p. 533), and acetone (Heer and Miescher, *Helv. Chim. Acta*, 1948, **31**, 1289) have been employed to promote the dehydrogenation of various donors; but most of these reactions undoubtedly take place in two distinct steps since they were generally carried out under conditions under which dehydrogenation of the donors occurs even in the absence of acceptor; the donor merely acts as a convenient source of hydrogen, or the acceptor helps to remove hydrogen from the catalyst. Possible evidence for direct hydrogen transfer was, however, obtained by Wieland (*Ber.*, 1912, **45**,

TABLE 1. *Transfer-hydrogenation of ethylenic compounds with* cyclo*hexene in the presence of palladium.**

Acceptor	Product	Donor (mols.)	Time (hr.)	Yield (%)
Allylbenzene	Propylbenzene	2	120	85
Propenylbenzene	,,	2	16	85
Indene	Indane	2	16	<10
,,	,,	6	528	95
trans-Stilbene	Dibenzyl	2	17	100
Tolan	*cis*-Stilbene	2	17	<10
,,	,,	12 †	1·5	70
,,	Dibenzyl	12 †	23	100
Acenaphthylene	Acenaphthene	20 †	15	100
1 : 1-Diphenylethylene	1 : 1-Diphenylethane	2	43	85
But-3-enoic acid	Butyric acid	1·4	73	90
Crotonic acid	,,	2	69	89
Oleic acid	Stearic acid	2	68	10
,,	,,	20 †	17	40
Sorbic acid	Hexenoic acid	2	70	70
,,	Hexanoic acid	20 †	17	90
Cinnamic acid	β-Phenylpropionic acid	2	64	90
Maleic acid	Succinic acid	0·5	80	50
,,	,,	2	15	100
Muconic acid	Adipic acid	20	30	80

* For details, see Experimental section. All reactions in tetrahydrofuran, except those marked † where no solvent was employed.

2606; 1913, **46**, 3327), who found that the dehydrogenation of glucose by palladium black was accelerated by benzoquinone or methylene-blue, and, while the present work was in progress, Bergmann and Eschinazi (*J. Amer. Chem. Soc.*, 1950, **72**, 5651) reported that mesityl oxide can be converted into isobutyl methyl ketone in 88% yield by menth-8-ene in the presence of a palladium–barium sulphate catalyst, whereas in the absence of the ketone rapid disproportionation to menthane and cymene takes place. Even in this case, however, the reaction was carried out at a temperature (140°) at which considerable dehydrogenation of the donor is observed.

In view of its ready disproportionation and availability, *cyclo*hexene is an obvious choice as a donor for metal-catalysed hydrogen-transfer reactions. We find that a wide range of ethylenic hydrocarbons and ethylenic acids undergo transfer-hydrogenation in high yields when heated with *cyclo*hexene at its boiling point or at that of a suitable solvent such as tetrahydrofuran, and a palladium catalyst (Table 1). As would be expected, benzenoid groups are not reduced and no transfer is observed with naphthalene, anthracene, or phenanthrene, whereas acenaphthylene is converted into acenaphthene. One acetylenic acceptor, tolan, has also been examined; as in catalytic hydrogenation with molecular hydrogen (Campbell and Campbell, *Chem. Reviews*, 1942, **31**, 77), *cis*-stilbene is the first product. Further reduction gives dibenzyl, the second stage being slower than the first.

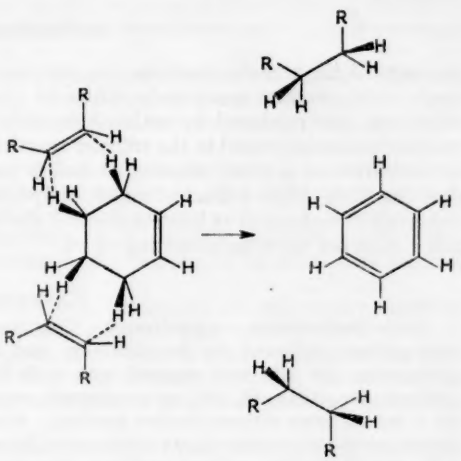


FIG. 3. *Schematic representation of hydrogen transfer between* cyclo*hexene and ethylenic acceptors.*

The transfer-hydrogenation of ethylenic and acetylenic compounds thus exhibits the same kind of specificity as catalytic hydrogenation with molecular hydrogen and it offers no important practical advantage with this type of acceptor, except that no special apparatus is required. Palladium black or other forms of palladium catalyst can be used, but Raney nickel is ineffective, although it catalyses the disproportionation of *cyclo*hexene (Corson and Ipatieff, *loc. cit.*). The *cyclo*hexadienes or 1 : 4-dihydronaphthalene can replace *cyclo*hexene as a donor; with maleic acid as the acceptor, the reaction times required are of the same order.

The stoicheiometry of the above reactions has not been examined in detail, but at least with one acceptor (maleic acid) 4 hydrogen atoms per *cyclo*hexene molecule and 2 hydrogen atoms per *cyclo*hexadiene or dihydronaphthalene molecule are available for transfer. In most cases, 2 molar proportions of *cyclo*hexene were employed, while in a few instances a large excess of *cyclo*hexene was necessary to effect appreciable reduction. These results are in accord with a picture of disproportionation and transfer as competing reactions on the catalyst surface. An important requisite for transfer will be co-adsorption of the donor and the acceptor. In a favourable case, these will be interspersed in the appropriate ratio, so that donor and acceptor molecules, but not two donor molecules, occupy adjacent positions and transfer will be facilitated, while disproportionation will be almost completely suppressed (Fig. 3). In less favourable cases where the acceptor is adsorbed much more strongly than the donor, the acceptor will act as a " poison " and effective co-adsorption only takes place if the donor is present in excess. Rate measurements in which the disappearance of *cyclo*hexene was followed quantitatively confirm (Table 2) that acceptors invariably decrease the rate of disproportionation and that transfer occurs more slowly than disproportionation in the absence of an acceptor. Moreover, of the acceptors listed in Table 1, those (*e.g.*, acenaphthylene) which require a large excess of *cyclo*hexene have a

much more marked retarding effect on disproportionation than those (*e.g.*, maleic acid) which undergo stoicheiometric transfer. Although a more detailed analysis must await direct measurement of adsorption, it appears that adsorption decreases in the sequence acenaphthylene>cinnamic acid>maleic acid>fumaric acid.

An interesting observation was made in the case of maleic acid. Although the catalyst, after being washed, was found to retain its activity, and although neither of the major

TABLE 2. *Effects of acceptors and non-acceptors on disproportionation of* cyclo*hexene. Initial first-order rate constants under comparable conditions.**

Acceptor	k (hr.$^{-1}$)	Acceptor	k (hr.$^{-1}$)	Non-acceptor	k (hr.$^{-1}$)
None	0·85	Cinnamic acid	0·08	None	0·85
Maleic acid	0·35	Acenaphthylene	0·02	Succinic acid	0·85
Fumaric acid	0·50			Maleic anhydride ...	<0·001
				Benzene	0·7

* See Experimental section.

products of the transfer reaction, *i.e.*, succinic acid and benzene, were inhibitors, yet the crude solid product completely inhibited the disproportionation of *cyclo*hexene. This effect was also produced by maleic anhydride, which does not undergo transfer, and the product-poisoning found in the transfer reaction with maleic acid is probably to be ascribed to formation of a small amount of maleic anhydride by dehydration. It is significant that the Diels–Alder adduct of maleic anhydride and *cyclo*hexa-1 : 3-diene, which might be expected to be formed at least in traces if the diene were an intermediate in disproportionation, does not show an inhibiting effect.

EXPERIMENTAL

Disproportionations.—cyclo*Hexene.* Commercial *cyclo*hexene was purified by refluxing over sodium, followed by fractionation, and had b. p. 82·5°/755 mm., n_D^{21} 1·4460. When *cyclo*hexene (10 ml.) was warmed with palladium black (100 mg.; prepared by Wieland's method, *Ber.*, 1912, **45**, 484) an exothermic reaction occurred and the liquid boiled vigorously for a few minutes without further heating. After 3 hours' refluxing, less than 0·3% of *cyclo*hexene remained, as shown by titration with bromine, and the liquid had n_D^{20} 1·4462, $\lambda_{max.}$ 2550 Å, $E_{1\,cm.}^{1\%}$ 9·0 (in EtOH), while a synthetic mixture of benzene (1 mol.) and *cyclo*hexane (2 mol.) had n_D^{20} 1·4490, $\lambda_{max.}$ 2550 Å, $E_{1\,cm.}^{1\%}$ 9·0. Treatment with chlorosulphonic acid gave benzenesulphonamide, m. p. 151°, in similar yields (49 and 52%, respectively) from the disproportionation product and the synthetic mixture. The unchanged residue was *cyclo*hexane, b. p. 80·5°/760 mm., n_D^{18} 1·4270. An identical result was obtained on carrying out the disproportionation in tetrahydrofuran.

1 : 4-*Dihydronaphthalene.*—1 : 4-Dihydronaphthalene (5 g.; m. p. 26°; prepared and purified according to Bamberger, *Ber.*, 1887, **20**, 3075, and Sand and Genssler, *Ber.*, 1903, **36**, 3705), palladium (100 mg.), and tetrahydrofuran (25 ml.) were heated under reflux for 40 hr. The solvent was removed through a column, and the residue treated with picric acid in ethanol, giving naphthalene picrate (5·3 g.), which was filtered off. The filtrate was diluted with water and extracted with chloroform. The extract was washed with sodium hydrogen carbonate and water, dried, and evaporated, giving tetralin (1·4 g.), b. p. 102°/20 mm., n_D^{21} 1·5433, identified as the sulphonamide, m. p. and mixed m. p. 135°.

1 : 2-*Dihydronaphthalene.* 1 : 2-Dihydronaphthalene (5 g.; m. p. −11°, n_D^{18} 1·5768; prepared by Strauss and Lemmel's method, *Ber.*, 1921, **54**, 25), palladium (0·1 g.), and tetrahydrofuran (25 ml.) were heated under reflux for 40 hr. Working up as above gave naphthalene picrate (6·7 g.) and tetralin (1·9 g.).

Transfer-hydrogenations with cyclo*Hexene.*—*Maleic acid.* (*a*) The acid (1·16 g.), *cyclo*hexene (1·64 g.), palladium (50 mg.), and tetrahydrofuran (25 ml.) were refluxed for 15 hr. After being filtered, the solution was evaporated, giving succinic acid (1·1 g.), m. p. and mixed m. p. 185—187°.

(*b*) A similar experiment with reflux for only 1 hr. gave, after oxidation with potassium permanganate in sulphuric acid, 0·5 g. (40%) of succinic acid.

(*c*) A similar experiment with 0·41 g. of *cyclo*hexene gave 0·63 g. (52%) of succinic acid after 80 hours' reflux.

(*d*) A similar experiment in which palladium was replaced by Raney nickel gave 0·05 g. (4%) of succinic acid after 72 hours' refluxing.

Crotonic acid. The acid (1·7 g.), *cyclo*hexene (3·3 g.), palladium black (50 mg.), and tetrahydrofuran (25 ml.) were refluxed for 69 hr. The product was an oil (1·7 g.), b. p. 160—170°, n_D^{23} 1·4050, which contained 11% of crotonic acid as indicated by titration with potassium permanganate, and gave butyranilide, m. p. and mixed m. p. 95°.

But-3-enoic acid. The acid (3·4 g.), *cyclo*hexene (5 g.), palladium (50 mg.), and tetrahydrofuran (25 ml.) were refluxed for 73 hr. Fractionation gave butyric acid (3·1 g.), b. p. 61—63°/12 mm., n_D^{22} 1·4002 (anilide, m. p. 96°).

Oleic acid. (*a*) The acid (2·8 g.), *cyclo*hexene (1·6 g.), palladium (50 mg.), and tetrahydrofuran (25 ml.) were refluxed for 68 hr. Removal of the catalyst and solvent gave a product (2·8 g.) of m. p. 39—41°, corresponding to a 9 : 1 mixture of oleic and stearic acid (Smith, *J.*, 1939, 975). This composition was confirmed by titration with bromine in chloroform.

(*b*) The acid (2·8 g.), *cyclo*hexene (25 ml.), and palladium (100 mg.) were refluxed for 17 hr. Removal of catalyst and distillation gave a product, m. p. 50—52°. This corresponds to a 7 : 3 mixture of oleic and stearic acid (Smith, *loc. cit.*), whereas bromine titration indicated a 60% content of oleic acid. Bromine titration of this distillate showed only *ca.* 2% of unchanged *cyclo*hexene.

Cinnamic acid. The acid (1·5 g.), palladium (50 mg.), *cyclo*hexene (1·6 g.), and tetrahydrofuran (25 ml.) were refluxed for 64 hr. Removal of the solvent and catalyst gave 1·4 g. of product, m. p. 43—44°, raised by one crystallisation from light petroleum (b. p. 40—60°) to 48°, the m. p. of pure β-phenylpropionic acid.

Sorbic acid. (*a*) The acid (1·1 g.), *cyclo*hexene (1·6 g.), palladium (50 mg.), and tetrahydrofuran (25 ml.) were refluxed for 70 hr. The product was an oil, n_D^{23} 1·4320, which contained less than 1% of sorbic acid, as shown by its ultra-violet light absorption ($E_{1\,cm.}^{1\%}$ 4·5 at 2580 Å); it consumed potassium permanganate corresponding to 0·7 ethylenic bond per mol., giving a 10% yield of succinic acid, and evidently consisted of a mixture of hexenoic and hexanoic acids.

(*b*) Sorbic acid (1·65 g.), palladium (100 mg.), and *cyclo*hexene (25 ml.) were refluxed for 17 hr., giving hexanoic acid (1·5 g.), n_D^{20} 1·4166 (anilide, m. p. 91—92°).

Muconic acid (with J. F. Smith). *cis* : *cis*-Muconic acid (0·5 g.), palladium (25 mg.), *cyclo*hexene (10 ml.), and tetrahydrofuran (15 ml.) were refluxed for 30 hr. Removal of the catalyst and solvent, followed by one recrystallisation of the residue from water, gave adipic acid (0·4 g.), m. p. and mixed m. p. 150°.

Allylbenzene. Allylbenzene (3·4 g.), palladium (50 mg.), *cyclo*hexene (3·3 g.), and tetrahydrofuran (25 ml.) were refluxed for 120 hr. Removal of the catalyst and fractionation gave propylbenzene (2·9 g.), b. p. 53—54°/18 mm., n_D^{21} 1·4910 (sulphonamide, m. p. 108—109°).

Propenylbenzene. Propenylbenzene (2·4 g.; b. p. 180°/747 mm., $\lambda_{max.}$ 2480 Å, ε 16,000 in EtOH), palladium (50 mg.), *cyclo*hexene (3·3 g.), and tetrahydrofuran (25 ml.) were refluxed for 16 hr. Removal of the catalyst and fractionation afforded *n*-propylbenzene (2·1 g.), b. p. 81—82°/50 mm., n_D^{20} 1·4915, ε 80 at 2480 Å (sulphonamide, m. p. 109—110°).

1 : 1-*Diphenylethylene.* 1 : 1-Diphenylethylene (3·6 g.; b. p. 115—116°/3 mm., n_D^{11} 1·6131), palladium (50 mg.), *cyclo*hexene (3·3 g.), and tetrahydrofuran (25 ml.) were refluxed for 43 hr. Removal of the solvent and catalyst, and fractionation, gave 1 : 1-diphenylethane (3·0 g.), b. p. 136—138°/12 mm., n_D^{14} 1·5780.

Stilbene. *trans*-Stilbene (0·9 g.), palladium (50 mg.), *cyclo*hexene (0·8 g.), and tetrahydrofuran (25 ml.) were refluxed for 17 hr. Removal of the catalyst and solvent gave dibenzyl (0·9 g.), m. p. and mixed m. p. 51°.

Tolan. (*a*) Tolan (0·9 g.; m. p. 61—62°) was subjected to the conditions of the preceding experiment. Mainly unchanged material (0·7 g.; m. p. 58—63°) was obtained.

(*b*) Tolan (2·0 g.), palladium (50 mg.), and *cyclo*hexene (15 ml.) were refluxed together, the progress of the reaction being followed by evaporating aliquots of the solution. After 23 hr., the products were homogeneous and removal of solvent and catalyst gave pure dibenzyl (2·0 g.), m. p. 51°.

(*c*) The above experiment was repeated, except that the reaction was interrupted after 1½ hr., the products being then completely liquid at room temperature. Distillation gave *cis*-stilbene (1·4 g.) b. p. 101—102°/1 mm., n_D^{22} 1·6195, which formed (±)-2 : 3-dibromo-1 : 4-diphenylbutane, m. p. 110—111°, on treatment with bromine in ether (cf. Buckles, *J. Amer. Chem. Soc.*, 1949, **71**, 1157).

Indene. (*a*) Indene (2·3 g.; b. p. 68°/15 mm., n_D^{22} 1·5746; freshly generated from the picrate), palladium (50 mg.), *cyclo*hexene (1·6 g.), and tetrahydrofuran (25 ml.) were refluxed for 16 hr. Removal of the catalyst and fractionation gave unchanged indene (2·0 g.).

(*b*) The above experiment was repeated, but with 4·9 g. of *cyclo*hexene and refluxing for 528 hr. The product (2·2 g.), b. p. 59—60°/12 mm., n_D^{16} 1·5312, showed no rapid reaction with bromine in chloroform and was almost pure indane, which formed a sulphonamide, m. p. 134—135°.

Acenaphthylene. Acenaphthylene (1·0 g.; m. p. 85°), palladium (50 mg.), and *cyclo*hexene (15 ml.) were refluxed for 15 hr., after which the solution was colourless. Removal of the catalyst and solvent gave acenaphthene (1·0 g.), m. p. 94—95° (picrate, m. p. and mixed m. p. 161°).

No transfer took place in a similar experiment in which palladium was omitted.

Naphthalene. Naphthalene was recovered unchanged after 1 g. had been refluxed with palladium (50 mg.) and *cyclo*hexene (25 ml.) for 90 hr. No evidence of transfer was also obtained with anthracene, phenanthrene, or fluoranthene under similar conditions.

Transfer-hydrogenations with Other Donors.—Maleic acid and cyclo*hexa*-1 : 3-*diene.* The acid (1 g.), the diene (1 g.), palladium (50 mg.), and tetrahydrofuran (25 ml.) were refluxed for 75 hr. Removal of the catalyst and solvent, and crystallisation of the residue from water, gave fumaric acid, m. p. >280°. The aqueous solution was oxidised with potassium permanganate and sulphuric acid, giving succinic acid (0·6 g.), m. p. and mixed m. p. 185°.

Maleic acid and 1 : 4-*dihydronaphthalene.* The acid (4·5 g.), 1 : 4-dihydronaphthalene (5·0 g.), palladium (0·1 g.), and tetrahydrofuran (25 ml.) were refluxed for 46 hr. The catalyst was filtered off, and the solution was diluted with ether (50 ml.) and extracted with 10% aqueous sodium hydroxide (33 ml.). The alkaline extract was acidified and extracted with ether, the ether was evaporated, and the product (3·5 g.) was oxidised as above, giving succinic acid (1·6 g.), m. p. 185—186°.

Rate Measurements.—General procedure. The solutions of the reactants in tetrahydrofuran were refluxed (b. p. *ca.* 65°) with the palladium-black catalyst in a closed reaction vessel. The rate of disappearance of *cyclo*hexene was determined by withdrawing 1-ml. samples at appropriate intervals, adding excess of bromine in carbon tetrachloride, and back-titrating the solution with aqueous sodium thiosulphate. With any one batch of catalyst, the results, only a selection of which are recorded in detail below, were reasonably consistent, considering the difficulty of exactly reproducing conditions in such a system. A number of runs were also carried out in which the *cyclo*hexene content was estimated by quantitative hydrogenation; the results are in good agreement but the method is less convenient. A third procedure consists of estimating the benzene formed by ultra-violet spectrometry; this will be described later.

Disproportionation of cyclo*hexene.* Under the conditions used, the order of the reaction with respect to *cyclo*hexene varied between 1 and 2, but for convenient comparison the results are expressed as first-order rate constants. The rate constants were approximately proportional to the amount of catalyst. The following runs refer to M-solutions of *cyclo*hexene in boiling tetrahydrofuran (25 ml.) at *ca.* 65° with (i) 10 mg., (ii) 25 mg., (iii) 40 mg., and (iv) 50 mg. of palladium. x is the volume (ml.) of 0·232M-bromine consumed by 1 ml. after t min.

(i) t	0	12	23	29	35	41	49	58	100	1400
x	4·20	3·74	3·32	3·08	2·90	2·71	2·57	2·36	1·88	0·66
10^2k_1 (min.$^{-1}$)	—	0·9	1·0	1·0	1·0	1·0	1·0	1·0	1·8	—
(ii) t	0	11	19	26	36	45	58	73	196	
x	3·90	3·13	2·52	2·06	1·64	1·38	1·15	0·94	0·38	
10^2k_1 (min.$^{-1}$)	—	1·9	2·2	2·4	2·4	2·3	2·1	1·9	—	
(iii) t	0	8	16	22	28	35	41	53	360	
x	4·20	3·07	2·21	1·73	1·39	1·17	1·00	0·80	0·29	
10^2k_1 (min.$^{-1}$)	—	4·0	4·1	4·0	3·9	3·7	3·5	3·1	—	
(iv) t	0	10	17	23	30	37	44	56	156	
x	4·30	2·54	1·88	1·51	1·21	0·98	0·82	0·60	0·16	
10^2k_1 (min.$^{-1}$)	—	5·3	4·9	4·7	4·3	4·0	3·8	3·5	—	

Effects of acceptors. The following runs were carried out with solutions M with respect to *cyclo*hexene and 0·5M with respect to acceptor in boiling tetrahydrofuran (25 ml.) containing 50 mg. of palladium. x is the volume (ml.) of 0·05M-bromine consumed by 1 ml. after t hours.

(i) No acceptor:

t	0	0·5	1	1·5	3	4·5	10
x	19·7	12·8	8·4	6·4	3·2	1·2	0·3
k_1 (hr.$^{-1}$)	—	0·87	0·85	0·76	0·61	0·62	—

(ii) With maleic acid :

t	0	0·5	1	3	6	23
x	20·0	16·7	14·1	13·1	12·7	11·4
k_1 (hr.$^{-1}$)	—	0·35	0·35	0·14	0·075	0·023

The catalyst from this run, after being washed with tetrahydrofuran, still caused disproportionation of *cyclo*hexene, at about one-third of the rate of (i). The solid product obtained from (ii) by evaporation of the solvent almost completely arrested the disproportionation of a fresh solution of *cyclo*hexene in the presence of fresh catalyst.

(iii) With fumaric acid :

t	0	1	2	3	17	40
x	20·0	12·5	6·8	4·2	0·5	0·1
k_1 (hr.$^{-1}$)	—	0·47	0·54	0·52	0·20	—

(iv) With cinnamic acid :

t	0	0·5	5	10	28
x	19·7	19·0	14·3	10·1	0·6
k_1 (hr.$^{-1}$)	—	0·078	0·062	0·067	—

(v) With acenaphthylene :

t	0	2	4	20	45	69	117
x	29·5	28·5	28·3	28·0	26·5	24·4	20·8
k_1 (hr.$^{-1}$)	—	0·024	0·017	0·0042	0·0037	0·0043	0·0049

Effects of non-acceptors. The following runs were carried out under the same conditions as the foregoing series.

(i) With succinic acid :

t	0	0·5	1	3	21
x	20·1	13·2	8·5	3·2	0·3
k_1 (hr.$^{-1}$)	—	0·85	0·86	0·61	—

(ii) With benzene :

t	0	1	2	3	5	16
x	19·9	10·0	5·8	4·1	2·0	0·4
k_1 (hr.$^{-1}$)	—	0·69	0·62	0·72	0·46	—

(iii) With maleic anhydride :

t	0	1	2	6	10	19
x	19·9	19·8	19·9	19·8	19·8	19·8
k_1 (hr.$^{-1}$)	—		<0·001			—

Grateful acknowledgment is made to the Blackburn Education Committee for a grant (to P. W. D. M.).

Department of Organic Chemistry,
Imperial College of Science and Technology,
South Kensington, London, S.W.7.

[*Received, February 24th*, 1954.]

Hydrogen Transfer. Part VII. Metal-catalysed Transfer-hydrogenation of Nitro-compounds.*

By E. A. Braude, R. P. Linstead, and K. R. H. Wooldridge.

[Reprint Order No. 5158.]

Transfer-hydrogenation, with *cyclo*hexene as a hydrogen donor and palladium as a catalyst, provides a convenient general method for the conversion of aliphatic and aromatic nitro-compounds into primary amines. In the presence of more than one functional group, transfer-hydrogenation is often remarkably selective and affords higher yields than direct catalytic hydrogenation or other methods of reduction. A mechanism is proposed which accounts for the difference in specificity in terms of surface-stereochemical effects.

In Part VI,* the transfer-hydrogenation of ethylenic and acetylenic compounds, with *cyclo*hexene as a donor, was described. The present paper deals with the application of this novel method of reduction to nitro-compounds which, we find, are converted into primary amines, generally in high yields. With this class of acceptor, the method is not merely of theoretical interest, but possesses considerable practical advantages and exhibits certain useful differences in specificity from conventional catalytic hydrogenation and other methods of reduction.

In order to establish optimum experimental conditions, the transfer-hydrogenations of nitrobenzene to aniline and *p*-nitrotoluene to *p*-toluidine were studied in some detail.

(1) *Stoicheiometry.*—Almost quantitative yields could be obtained by using only the theoretical amounts (*i.e.*, 1·5 mols.) of *cyclo*hexene and the rate of transfer shows little increase at higher *cyclo*hexene concentrations, although transfer takes place much more slowly than disproportionation in the absence of foreign acceptor. (Under comparable conditions, in boiling tetrahydrofuran, the half-times are *ca.* 15 hr. and 20 min., respectively.) This shows that the disproportionation of the donor is almost entirely suppressed by the nitro-compound, as it is by some ethylenic acceptors (*e.g.*, maleic acid; Part VI).

(2) *Solvents.*—Although water is formed in the reaction, the use of *cyclo*hexene alone or with other water-immiscible solvents, such as benzene or *cyclo*hexane, is satisfactory in small-scale experiments. For larger-scale experiments, the addition of water-miscible solvents such as methanol, ethanol, or tetrahydrofuran is advantageous; the rate of transfer decreases with increasing dilution, but is of the same order in boiling solvents of similar boiling points (*e.g.*, ethanol, benzene, and *cyclo*hexane, cf. p. 3591). Even in diethyl ether (b. p. 35°) and tetrahydrofuran (b. p. 65°) the rates differ by a factor of less than two, showing that the temperature coefficient is very small and corresponds to an apparent energy of activation of less than 5 kcal./mole. A somewhat reduced rate of transfer is found in acetic acid; this appears to be a specific solvent effect which has also been encountered in the direct catalytic reduction of nitro-compounds (Adams, Cohen, and Rees, *J. Amer. Chem. Soc.*, 1927, **49**, 1093; Line, Wyatt, and Smith, *ibid.*, 1952, **74**, 1808; Iffland and Cassis, *ibid.*, p. 6284; Smith and Bedoit, *J. Phys. Colloid Chem.*, 1951, **55**, 1085). An essential condition, which has a more marked influence than either solvent or temperature variation, is vigorous ebullition. If the reaction mixture, instead of being refluxed, is mechanically stirred at a temperature below the boiling point, the reaction comes to a standstill after 10—20% transfer (Fig. 1); this is not due to preferential disproportionation of the donor under such conditions, since the addition of more *cyclo*hexene is without effect. Somewhat similar observations were made with dehydrogenation reactions by Linstead and Michaelis (*J.*, 1940, 1134) who found that boiling tetralin is dehydrogenated over palladium at 180°, but undergoes little change under tranquil conditions at 200°. It was suggested that the mechanical effect of boiling helps to detach hydrogen from the catalyst surface and thus promotes further reaction, and a similar explanation may be offered in the present case

* Part VI, preceding paper.

if it is assumed that the amine formed is strongly chemisorbed and that ebullition promotes the transport of reactants and products towards and away from the catalyst surface. A possible alternative explanation is that, in virtue of the greater volatility of *cyclo*hexene than of the nitro-compound, a more favourable adsorption ratio is set up under ebullescent conditions.

(3) *Catalysts.*—Palladium is equally effective in a colloidal form, or deposited chemically on charcoal, calcium carbonate, or alumina, or deposited electrolytically on platinum foil, and the rate of transfer shows only slight dependence on the amount of catalyst, provided the ratio of palladium to reactants is not less than *ca.* 10^{-3}. In practice, a ratio of 10^{-2} was found convenient. Much lower yields are obtained with platinum, and it is of interest that platinum is also reported to be less effective than palladium in the direct hydrogenation of nitro-compounds at atmospheric pressure (Brand and Steiner, *Ber.*, 1922, **55**, 875; Rampino and Nord, *J. Amer. Chem. Soc.*, 1941, **63**, 2745; Streltsova and Zelinski, *Bull. Acad. Sci., U.R.S.S.*, 1941, 401; 1943, 56). As with ethylenic acceptors (Part VI), Raney nickel has only negligible activity under the conditions tried, although it catalyses both the disproportionation of *cyclo*hexene (Corson and Ipatieff, *J. Amer. Chem. Soc.*, 1939, **61**, 1056) and the direct hydrogenation of nitro-compounds (*e.g.*, Lieber *et al.*, *J. Amer. Chem. Soc.*,

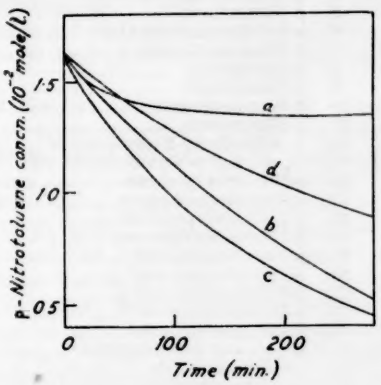


FIG. 1. *Rates of reduction of* p-*nitrotoluene by* cyclo*hexene on palladium.*

(a) *In ethanol at* 55·7°.
(b) *In methanol at* 64°.
(c) *In ethanol at* 78°.
(d) *Repeat run in ethanol at* 78°.

(*For details, see Experimental section.*)

1939, **61**, 384; 1949, **71**, 1515; 1950, **72**, 1190; Johnson and Degering, *ibid.*, 1939, **61**, 3194; Winans, *ibid.*, 1939, **61**, 3564; Samuelsen, Vladimir, Garik, and Smith, *ibid.*, 1950, **72**, 3872; Albert and Ritchie, *J. Proc. Roy. Soc. N.S.W.*, 1940, **74**, 74; Allison, Comte, and Fierz-David, *Helv. Chim. Acta*, 1951, **34**, 818).

TABLE 1. *Transfer-hydrogenation of* p-*nitrotoluene.**

Donor	Solvent	Temp.	Time (hr.)	Transfer (%)
*cyclo*Hexene	Excess of *cyclo*hexene	83°	17	96
,,	Ethanol	78	17	95
,,	Tetrahydrofuran	65	15	85
1-Methyl*cyclo*hexene	Ethanol	78	18	8
4-Methyl*cyclo*hexene	Ethanol	78	18	72
1 : 4-Dihydrophthalic acid	Tetrahydrofuran	65	17	45
Limonene †	None	175	8	15

* For details of conditions, see Experimental section. † With nitrobenzene as acceptor.

A number of other donors were tested against *p*-nitrotoluene, but none was as effective as *cyclo*hexene (Table 1), although disproportionation was again almost completely suppressed in the presence of the acceptor. Thus, 4-methyl*cyclo*hexene gave 72% of *p*-toluidine and 88% of toluene after 17 hours' refluxing in tetrahydrofuran. No transfer took place in boiling ethanol with tetralin, *cyclo*pentene, *cyclo*pent-1-enecarboxylic acid, *cyclo*heptene, *cyclo*octene, or *cyclo*hexanone, and it is significant that none of these compounds undergoes disproportionation under such conditions.

The only examples of catalysed transfer-hydrogenation of nitro-compounds which could be found in the literature involve as donors either hydrazine (Busch and Schulz, *Ber.*, 1929, **62**, 1458; Kuhn, *J. Amer. Chem. Soc.*, 1951, **73**, 1510; Balcolm and Furst, *ibid.*, 1953, **75**, 4334) which gave azoxy-, azo-, and hydrazo-compounds as well as amines, or alcohols and hydrocarbons (Legg and Adam, B.P. 166,283; Castner and Lawson, U.S.P. 2,377,071; *Chem. Abs.*, 1945, **39**, 4093) which have been used only at high temperatures (>250°).

The results of the transfer-hydrogenation of a wide range of nitro-compounds with *cyclo*hexene are summarised in Tables 2 and 3. Mononitro-compounds containing hydroxyl, alkoxyl, keto-, carboxyl, or cyano-substituents give the corresponding amines, these functional groups remaining unchanged. The yields often compare favourably with

TABLE 2. *Transfer-hydrogenation of mononitro-compounds to amines with* cyclo*hexene and palladium.**

No.	Nitro-compound	Solvent	Time (hr.)	Yield (%)
1.	Nitropropane	Ether	72	55
2.	Nitrobenzene	Ethanol	17	93
3.	*o*-Nitrotoluene	,,	17	100
4.	*m*-Nitrotoluene	,,	17	65
5.	*p*-Nitrotoluene	,,	17	95
6.	*p-tert.*-Butylnitrobenzene	None	40	54
7.	1-Nitronaphthalene	Ethanol	135	71
8.	*o*-Nitrophenol	Tetrahydrofuran	9	88
9.	*p*-Nitrophenol	,,	9	51
10.	2-Nitroresorcinol	,,	12	17
11.	*p*-Nitroanisole	None	17	83
12.	1 : 4-Diethoxy-2-nitrobenzene	,,	14	96
13—15.	*o*-, *m*-, and *p*-Nitrobenzaldehyde	Ethanol	17	<10
16.	*o*-Nitroacetophenone	,,	24	89
17.	*m*-Nitroacetophenone	,,	48	75
18.	*p*-Nitroacetophenone	None	24	98
19.	1-Nitroanthraquinone	Tetrahydrofuran	17	58
20.	*o*-Nitrobenzoic acid	Ethanol	17	92
21.	*m*-Nitrobenzoic acid	,,	17	58
22.	*p*-Nitrobenzoic acid	,,	17	96
23.	*o*-Nitrobenzonitrile	Tetrahydrofuran	40	59
24.	*m*-Nitrobenzonitrile	,,	40	87
25—27.	*o*-, *m*-, and *p*-Nitroaniline	Ethanol	17	< 2
28.	*o*-Nitroacetanilide	,,	17	100
29.	*m*-Nitroacetanilide	,,	17	81
30.	*p*-Nitroacetanilide	,,	17	27
31.	*NN*-Dimethyl-*m*-nitroaniline	None	20	73
32.	*p*-Bromonitrobenzene	,,	17	< 2
33.	2-Nitrothiophen	,,	90	< 2

* For details see Experimental section.

TABLE 3. *Transfer-hydrogenation of polynitro-compounds.**

No.	Compound	Solvent	Time (hr.)	Product	Yield (%)
34.	*o*-Dinitrobenzene	Ethanol	5	*o*-Nitroaniline	<2
35.	*m*-Dinitrobenzene	Tetrahydrofuran	15	*m*-Nitroaniline	80
36.	*p*-Dinitrobenzene	,,	19	*p*-Nitroaniline	<2
37.	2 : 4-Dinitrotoluene	—	40	2 : 4-Diaminotoluene	75
38.	1-*tert.*-Butyl-2 : 4-dinitrobenzene	—	36	2 : 4-Diamino-1-*tert.*-butylbenzene	95
39.	1 : 8-Dinitronaphthalene	—	17	1 : 8-Diaminonaphthalene	97
40.	2 : 4-Dinitrophenol	Ethanol	48	2 : 4-Diaminophenol	65
41.	3 : 5-Dinitrobenzoic acid	,,	17	3-Amino-5-nitrobenzoic acid	60
42.	1 : 3 : 5-Trinitrobenzene	—	120	3 : 5-Dinitroaniline	9
43.	2 : 4 : 6-Trinitrotoluene	Ethanol	41	4-Amino-2 : 6-dinitrotoluene 2-Amino-4 : 6-dinitrotoluene	11 9
44.	Picric acid	Tetrahydrofuran	14	Picramic acid	28

* For details see Experimental section.

those obtained by other methods; thus, *o*-nitroacetophenone gives 95% of *o*-aminoacetophenone, whereas the yields reported for direct catalytic hydrogenation and reduction by tin and hydrochloric acid are 75 and 68%, respectively (Boyd and Leonard, *J. Org. Chem.*, 1946, **11**, 405; Camps, *Arch. Pharm.*, 1902, **240**, 1). On the other hand, hardly any reduction occurs with the three nitroanilines, *p*-bromonitrobenzene, the three nitrobenzaldehydes, and 2-nitrothiophen. Thiophen derivatives are well-known catalyst " poisons " and the nitrobenzaldehydes also resist direct catalytic hydrogenation owing to formation of polymeric products (cf. Phillips and Maggiole, *J. Org. Chem.*, 1950, **15**, 659), but *m*-nitroaniline is smoothly converted into *m*-phenylenediamine, and *p*-bromonitrobenzene into aniline hydrobromide by hydrogen in the presence of palladium, as observed by earlier workers (Rosenmund and Zetsche, *Ber.*, 1918, **51**, 578; Brand and Steiner, *loc. cit.*; Streltsova and Zelinski, *locc. cit.*). The selectivity of transfer-hydrogenation is thus considerably more marked than that of direct catalytic hydrogenation and is further illustrated by the fact that, in contrast to the nitroanilines, the nitroacetanilides and *NN*-dimethyl-*m*-nitroaniline are readily reduced.

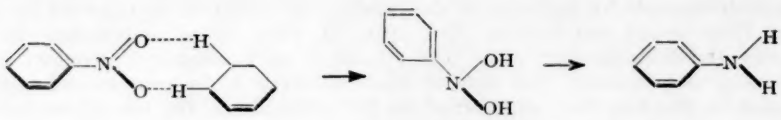
Polynitro-compounds exhibit an even greater specificity. Transfer-hydrogenation of *m*-dinitrobenzene gives exclusively *m*-nitroaniline, as would be expected from the behaviour of the product, but the two alkylated *m*-dinitrobenzenes (Table 3) and 1 : 8-dinitronaphthalene give the diamines in excellent yields. 2 : 4-Dinitrophenol also gives the diamine, whereas only one nitro-group is reduced in 3 : 5-dinitrobenzoic acid and in trinitro-derivatives.

The results summarised in the Tables show that, in addition to cases of complete selectivity, the ease of transfer-hydrogenation of nitro-compounds is very sensitive to structural variations in the acceptor, in contrast to direct reduction with hydrogen on palladium or platinum catalysts where substituents are reported to have relatively little effect on the rate of reaction (Adams *et al.*, *loc. cit.*; Streltsova and Zelinski, *loc. cit.*, 1943; Dunsworth and Nord, *J. Amer. Chem. Soc.*, 1950, **72**, 4197). This lends support to the view (Part VI) that transfer-hydrogenation does not consist of separate donor-dehydrogenation and acceptor-hydrogenation steps, but is a linked process involving specific donor–acceptor relations. It could be suggested that differences observed are primarily due to " poisoning " effects of the acceptors or their reduction products on the disproportionation or dehydrogenation of the donor. That this is not the case is illustrated by the fact that neither *m*-nitroaniline nor *m*-phenylenediamine inhibits the disproportionation of *cyclo*hexene, although they do have a retarding effect. The non-reactivity of *m*-nitroaniline (and presumably of other compounds which undergo direct catalytic hydrogenation) must therefore be due to a lack of acceptor properties, which could conceivably arise from such causes as (i) non-adsorption on the catalyst, (ii) unsuitable orientation on the catalyst surface, and (iii) intrinsically low reduction potential. Since other compounds containing free amino-groups as well as alkylated derivatives of *m*-nitroaniline are readily reduced by transfer-hydrogenation it is difficult to believe that effects of type (i) or (iii) can be primarily responsible. The marked differences in rate produced by various substitutents (Table 1) also cannot be rationalised in terms of usual electronic influences. The most probable cause of the lack of acceptor properties of *m*-nitroaniline is (ii), and the effect of other substituents may also be visualised in terms of the surface-stereochemical requirements of the reaction.

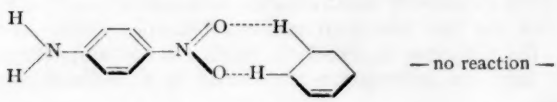
A variety of partly reduced derivatives, particularly hydroxylamines and nitroso-compounds, have been postulated as intermediates in the conversion of nitro-compounds into amines under different conditions (cf. Haber, *Z. physikal. Chem.*, 1900, **32**, 193), and phenylhydroxylamine has been isolated on hydrogenation of nitrobenzene over palladium (Brand and Steiner, *loc. cit.*). Phenylhydroxylamine is also reduced to aniline by *cyclo*hexene and palladium, but nitrosobenzene gave only intractable products. This evidence does not necessarily exclude nitroso-derivatives as intermediates, since they may exert concentration-dependent poisoning effects, but it does render their intervention unlikely in the present case. A plausible reaction course, which does not appear to have been previously considered and does not entail free nitroso-intermediates, involves as a first step the addition of two hydrogen atoms to give either the hydroxylamine *N*-oxide O←NHR·OH

or the isomeric dihydroxyamine (nitroso-hydrate) $R{\cdot}N(OH)_2$, followed by hydrogenolysis of the N–O bonds. On this basis, a tentative interpretation of the remarkable difference in specificity observed in transfer-hydrogenation may be given. The first step may be represented as in Fig. 2*a* with the nitro-group initially lying flat on the catalyst surface alongside a donor molecule. As $-NO_2$ is converted into $-N(OH)_2$, the nitrogen atom passes from a planar to a tetrahedral valency-bond configuration, and whereas in the nitro-compound the nitro- and phenyl groups are essentially uniplanar (cf. Hodgkin and

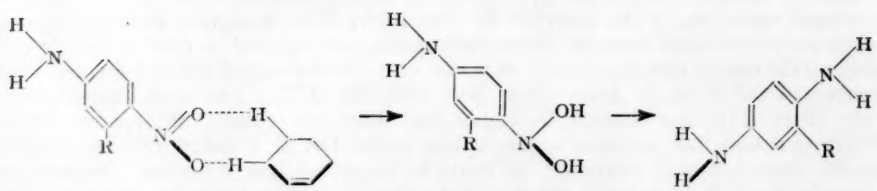
FIG. 2.



(*a*) *Catalytic transfer-hydrogenation of nitrobenzene* (*schematic*).



(*b*) *Inhibition of hydrogen-transfer to* p-*nitroaniline* (*schematic*).



(*c*) *Hydrogen-transfer to* p-*nitroaniline containing a bulky substituent* ortho *to the nitro-group* (*schematic*).

Pitt, *Ann. Reports*, 1950, **47**, 455), in the dihydroxy-amine, the benzene ring and the two oxygen atoms can no longer simultaneously retain their positions on the catalyst surface. Normally, the benzene ring will be lifted off the surface, while the $-N(OH)_2$ group will remain preferentially adsorbed, thus allowing the reduction to go to completion by subsequent hydrogenolysis (Fig. 2*a*). If, however, the benzene ring carries another substituent (*e.g.*, NH_2) which also has a strong affinity for the catalyst, the chemisorptive forces acting on the ring may exceed those acting on the nitro-group. In this case, the plane of the benzene ring will remain parallel to the catalyst surface, while one or both N–O links of the nitro-group undergoing reduction will be forced to become directed away from the surface and transfer will be inhibited (Fig. 2*b*). But if now an additional substituent (*e.g.*, *tert.*-butyl) is introduced, sufficiently bulky to prevent the benzene ring from lying flat on the catalyst surface, hydrogen transfer will again be possible, even in the presence of a strongly chemisorbed group such as NH_2 (Fig. 2*c*). This phenomenon may be termed " positive catalyst hindrance " and compared with the " negative catalyst hindrance " encountered in direct catalytic hydrogenation (Linstead, Doering, Davis, Levine, and Whetstone, *J. Amer. Chem. Soc.*, 1942, **64**, 1985).

EXPERIMENTAL

Materials.—The nitro-compounds were either purified commercial specimens or prepared by the methods indicated below. *cyclo*Hexene was distilled from sodium and stored in the dark. Tetrahydrofuran was refluxed with potassium hydroxide for several hours and then fractionated. Commercial absolute ethanol was used without purification. Palladium black was prepared by Wieland's method (*Ber.*, 1912, **45**, 484); it is important to add the formic acid immediately

after the sodium hydroxide otherwise a dark brown catalyst instead of the more active black form results. Palladised charcoal was prepared by the method of Linstead and Thomas (*J.*, 1940, 1130).

Transfer-hydrogenation of p-*Nitrotoluene.*—(a) *General procedure.* *p*-Nitrotoluene (2·5 g.), *cyclo*hexene (4·5 g.) and palladium black (20 mg.) were heated under vigorous reflux for 17 hr. At the end of this time, the solution was practically colourless. The catalyst was filtered off and constituents boiling below 100° were removed on the steam-bath. The residue was dissolved in ether (100 ml.), the ether solution was dried ($MgSO_4$) and filtered, and anhydrous hydrogen chloride was passed in. The precipitate was washed with dry ether, giving *p*-toluidine hydrochloride (2·5 g., 96%), m. p. 235°. The base was liberated by aqueous sodium hydroxide and had m. p. 45° undepressed on admixture with an authentic specimen, and gave a benzoyl derivative, m. p. 158°.

(b) *Catalyst variation.* Yields of *p*-toluidine were reproducible within ±5% when the same batch of catalyst was used. The reproducibility of different batches of palladium black is illustrated below. 2·5 g. of nitrotoluene, 15 ml. of *cyclo*hexene and 20 mg. of catalyst were refluxed for 7 hr. in each case :

Batch number	1	2	3	4	5	6	7	8
Yield of *p*-toluidine (%)	90	89	69	86	70	74	60	77

Subsequently, the activity of each batch was checked against *p*-nitrotoluene under these conditions. Results obtained with other catalysts, with the same quantities of *p*-nitrotoluene and *cyclo*hexene, are shown below.

Catalyst	Amount (mg.)	Time (hr.)	Yield (%) of *p*-toluidine	Catalyst	Amount (mg.)	Time (hr.)	Yield (%) of *p*-toluidine
10% Pd–C	190	7	95	Pt black	20	7	18
1% Pd–$CaCO_3$ [a]	100	18	95	10% Pt–C	350	7	13
0·1% Pd–Al_2O_3	1000	18	64	PtO_2	45	17	0
$PdCl_2$	20	17	1	Raney Ni [c]	100	22	2
Pd–Pt [b]	10	13	100	W.7 Raney Ni [d]	100	100	2

[a] The catalyst was heated with boiling *cyclo*hexene for a few minutes before adding nitrotoluene. [b] 10 mg. of Pd deposited electrolytically (cf. Hamer and Acree, *J. Res. Nat. Bur. Stand.*, 1944, **33**, 87) on an 1 × 1″ Pt foil. [c] Mozingo, *Org. Synth.*, 1941, **21**, 15. [d] Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 695.

(c) *Solvent and concentration variation.* Except where otherwise indicated, the following experiments were all carried out with 2·5 g. of *p*-nitrotoluene, 4·6 g. (2 mols.) of *cyclo*hexene, 20 mg. of palladium black, and the solvent at the b. p. for 17 hr.

Solvent	Vol. (ml.)	Yield (%)	Solvent	Vol. (ml.)	Yield (%)
Ethanol	20	93	Acetone	50	90
,,	50	77	Acetic acid [1]	10	55
,,	125	73	*cyclo*Hexane	50	75
Ether	50	55	Benzene [2]	50	16
Tetrahydrofuran	50	85	Benzene [3]	50	73

[1] 14 g. of *cyclo*hexene. [2] "AnalaR." [3] Purified by treatment with Raney nickel and distillation.

With ethanol (125 ml.) as a solvent, the yield of *p*-toluidine was increased by less than 10% on increasing the amount of *cyclo*hexene from 1·5 to 6 mols., or the amount of catalyst from 20 to 80 mg.

When *p*-nitrotoluene (0·289 g.), *cyclo*hexene (0·390 g.), ethanol (50 ml.), and palladium black (20 mg.) were mechanically shaken at 30°, the extent of reduction, determined spectrometrically by the decrease in the intensity of the 2690-Å band (ε 9700), was 7% after 30 min. and 15% after 90 min. No further reduction was observed during 6 hr.

(d) *Donor variation.* *p*-Nitrotoluene (3·57 g.), 4-methyl*cyclo*hexene (2·60 g.; b. p. 102—104°, n_D^{20} 1·4443), ethanol (52 ml.), and palladium black (30 mg.) were heated under reflux for 18 hr. The catalyst was filtered off and the mixture distilled on the steam-bath. The distillate (50 ml.) had $\lambda_{max.}$ 2620 Å, $E_{1\,cm.}^{1\%}$ 1·00 corresponding to a toluene content of 4·6% (2·3 g., 88%). (Toluene in ethanol exhibits $\lambda_{max.}$ 2620 Å, $E_{1\,cm.}^{1\%}$ 22·0.) The residue was dissolved in ether, dried ($MgSO_4$), and treated with anhydrous hydrogen chloride, giving *p*-toluidine hydrochloride (1·82 g., 72%).

A similar experiment with 1-methyl*cyclo*hexene (b. p. 108—110°/756 mm., n_D^{15} 1·4541; cf. Vogel, *J.*, 1938, 1322) gave a distillate containing toluene (0·42 g., 18%) and furnished only 8% of *p*-toluidine hydrochloride.

p-Nitrotoluene (2·5 g.), 3 : 6-dihydrophthalic acid (0·81 g.), tetrahydrofuran (35 ml.), and palladium black (50 mg.) were heated under reflux for 17 hr. The catalyst and solvent were removed and the residue was dissolved in ether. The ethereal solution was extracted with 10% sodium hydroxide solution. The aqueous layer, on acidification with hydrochloric acid, gave phthalic acid (0·41 g., 50%), m. p. and mixed m. p. 206°. The ethereal layer was dried ($MgSO_4$) and anhydrous hydrogen chloride was passed in, giving *p*-toluidine hydrochloride (0·159 g., 45%), m. p. 235°.

No *p*-toluidine could be detected from the attempted reduction of *p*-nitrotoluene with the following (solvent and time in parentheses, palladium-black catalyst in all cases): *cyclo*pentene (ether, 25 hr.), *cyclo*pentene-1-carboxylic acid (tetrahydrofuran, 27 hr.), *cyclo*heptene (tetrahydrofuran, 27 hr.), *cyclo*octene (ethanol, 68 hr.), limonene (tetrahydrofuran, 10 hr.), tetralin (ethanol, 7 hr.), *cyclo*hexanol (tetrahydrofuran, 12 hr.).

Transfer-hydrogenation of Other Nitro-compounds.—(CH = *cyclo*hexene, Pd = palladium black. For % yields, see Tables 2 and 3, unless stated. Some of the lower yields are based on the results of single experiments and could undoubtedly be increased by prolonging the reaction time. Examples 34, 36, 42, and 43 were carried out by R. Chayen.)

1. Nitropropane (2·84 g.), CH (8 g.), ether (50 ml.), and Pd (50 mg.) after 72 hr. gave *n*-propylamine hydrochloride (1·63 g.) (derived picrate, m. p. 134°).

2. Nitrobenzene (61·5 g.), CH (90 ml.), and Pd (0·53 g.) were heated for 24 hr. under vigorous reflux. After being filtered from the catalyst, the solution was dried ($MgSO_4$) and fractionated through a short column, giving two main fractions: (i) (55 ml.), b. p. 77—79°/760 mm., n_D^{14} 1·4950, $\lambda_{max.}$ 2550 Å ($E^{1\%}_{1\,cm.}$ 26) in ethanol, which consisted largely of benzene ($\lambda_{max.}$ 2550 Å, $E^{1\%}_{1\,cm.}$ 27); (ii) (43 g.), b. p. 71—72°/14 mm., completely soluble in dilute hydrochloric acid, consisting entirely of aniline (93% yield). It was identified as the hydrochloride, m. p. 195°, and benzanilide, m. p. 160°.

3. *o*-Nitrotoluene (1·81 g.), CH (3·25 g.), ethanol (36 ml.), and Pd (15 mg.) were refluxed for 17 hr. The products were worked up as described above for *p*-nitrotoluene, giving *o*-toluidine hydrochloride (1·92 g.), m. p. 212° (benzoyl derivative, m. p. 144°).

4. *m*-Nitrotoluene (2·46 g.), CH (4·63 g.), ethanol (49 ml.), and Pd (49 mg.) after 17 hr. gave *m*-toluidine as the hydrochloride (1·70 g.) (benzoyl derivative, m. p. 124°).

6. *p-tert.*-Butylnitrobenzene (2 g.; Craig, *J. Amer. Chem. Soc.*, 1935, **57**, 195), CH (15 ml.), and Pd (24 mg.) after 40 hr. gave *p*-amino-*tert.*-butylbenzene as the hydrochloride (1·10 g.) (benzoyl derivative, m. p. 140°; Malherbe, *Ber.*, 1919, **52**, 322, gives m. p. 134—136°).

7. 1-Nitronaphthalene (2·10 g.), CH (3·5 g.), ethanol (44 ml.), and Pd (15 mg.) after 17 hr. gave 1-naphthylamine as the hydrochloride (0·51 g., 24%) (benzoyl derivative, m. p. 158°). After 135 hr., the yield was 1·58 g. (75%).

8. *o*-Nitrophenol (2·5 g.), CH (4·5 g.), tetrahydrofuran (25 ml.), and Pd (50 mg.) after 9 hr. gave *o*-aminophenol as the hydrochloride (2·3 g.) m. p. 201—203° (free base, m. p. 173°).

9. *p*-Nitrophenol (2·5 g.), CH (4·6 g.), tetrahydrofuran (25 ml.), and Pd (50 mg.) after 9 hr. gave *p*-aminophenol as the hydrochloride (1·27 g.) (free base, m. p. 184°).

10. 2-Nitroresorcinol (2 g.; Kaufmann and de Pay, *Ber.*, 1904, **37**, 725), CH (3·2 g.), tetrahydrofuran (25 ml.), and Pd (50 mg.) after 12 hr. gave unchanged nitroresorcinol (1·66 g., 83%) and 2-aminoresorcinol as the hydrochloride (0·35 g.).

11. *p*-Nitroanisole (2·5 g.), CH (5 g.), and Pd (17 mg.) after 17 hr. gave *p*-anisidine as the hydrochloride (2·17 g.) (free base, m. p. 57—58°; benzoyl derivative, m. p. 159°).

12. 1 : 4-Diethoxy-2-nitrobenzene (25 g.; m. p. 48°; supplied by Whiffen and Co. Ltd., through the courtesy of Dr. J. T. W. Mann), *cyclo*hexene (50 ml.), and 10% palladium–charcoal (1 g.) were heated under vigorous reflux until the solution was colourless (14 hr.). The catalyst was filtered off and the solution evaporated on the steam-bath. The colourless solid residue, m. p. 82—83°, was crystallised from dilute ethanol, giving 2 : 5-*diethoxyaniline* (20·5 g., 96%) m. p. 84° (Found: C, 66·3; H, 8·3; N, 7·8. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3; N, 7·7%).

13—15. Each of the nitrobenzaldehydes (2·5 g.), *cyclo*hexene (2·1 g.), and Pd (18 mg.) were refluxed for 65 hr. Unchanged aldehyde (>90%) was recovered in each case. A solution of *p*-nitrobenzaldehyde (2·5 g.) in ethanol (50 ml.) absorbed less than 5% of the calculated volume of hydrogen on shaking in the presence of Pd (20 mg.).

16. *o*-Nitroacetophenone (0·54 g.), CH (5 ml.), tetrahydrofuran (25 ml.), and Pd (50 mg.) after 17 hr. gave *o*-aminoacetophenone as the hydrochloride (0·50 g.), m. p. 167° (benzoyl

derivative, m. p. 98°; Bogert and Nabenhauer, *J. Amer. Chem. Soc.*, 1924, **46**, 1703, give 98°). A larger-scale run (0·5 mole) in ethanol gave a 95% yield.

17. *m*-Nitroacetophenone (2·5 g.), CH (3·7 g.), ethanol (50 ml.), and Pd (16 mg.) after 48 hr. gave *m*-aminoacetophenone as the hydrochloride (1·95 g.) (free base, m. p. 97°; Leonard and Boyd, *J. Org. Chem.*, 1946, **11**, 405, give m. p. 98—99°).

18. *p*-Nitroacetophenone (5 g.), CH (20 ml.), ethanol (20 ml.), and Pd (250 mg.) after 24 hr. gave *p*-aminoacetophenone (4 g.), m. p. 105°, unchanged on crystallisation from water [Derick and Bornmann (*J. Amer. Chem. Soc.*, 1925, **35**, 1286) give m. p. 110° (corr.)] (benzoyl derivative, m. p. 203°; Chattaway, *J.*, 1904, **386**, gives m. p. 205°).

19. 1-Nitroanthraquinone (2·5 g.), CH (15 g.), tetrahydrofuran (30 ml.), and Pd (50 mg.) after 17 hr. gave 1-aminoanthraquinone (1·35 g.), m. p. 244°.

20. *o*-Nitrobenzoic acid (2·5 g.), CH (3·7 g.), ethanol (50 ml.), and Pd (60 mg.) after 17 hr. gave anthranilic acid as the hydrochloride (2·4 g.) (free base, m. p. 146°).

21. *m*-Nitrobenzoic acid (2·5 g.), CH (3·7 g.), ethanol (20 ml.), and Pd (29 mg.) after 17 hr. gave *m*-aminobenzoic acid as the hydrochloride (1·5 g.) (free base, m. p. 173°).

22. *p*-Nitrobenzoic acid (2·5 g.), CH (3·7 g.), ethanol (50 ml.), and Pd (60 mg.) after 17 hr. gave *p*-aminobenzoic acid as the hydrochloride (2·45 g.) (free base, m. p. 187°).

23. *o*-Nitrobenzonitrile (3 g.; Bogert and Hand, *J. Amer. Chem. Soc.*, 1902, **24**, 1035), CH (14 g.), tetrahydrofuran (15 ml.), and Pd (30 mg.) after 40 hr. gave *o*-aminobenzonitrile as the hydrochloride (1·85 g.) (free base, m. p. 45°; acetyl derivative, m. p. 128°; Bogert and Hand, *loc. cit.*, give m. p. 132°).

24. *m*-Nitrobenzonitrile (4 g.), CH (18 g.), tetrahydrofuran (20 ml.), and Pd (40 mg.) after 40 hr. gave *m*-aminobenzonitrile as the hydrochloride (3·61 g.) [free base, m. p. 52°; benzoyl derivative, m. p. 141° (Bogert and Beans, *J. Amer. Chem. Soc.*, 1904, **26**, 464, give m. p. 141°)].

25. *o*-Nitroaniline (2·5 g.), CH (14 g.), and Pd (21 mg.) after 17 hr. gave only unchanged nitroaniline; no *o*-phenylenediamine could be detected by the quinoxaline test.

26. *m*-Nitroaniline (2·5 g.), *cyclo*hexene (14 g.), and Pd (100 mg.) after 52 hr. gave unchanged *m*-nitroaniline, m. p. 111°, which did not give a brown colour with dilute hydrochloric acid and potassium nitrite at 0°, whereas 2 mg. of *m*-phenylenediamine could be readily detected by this test under the same conditions. A solution of the same sample of *m*-nitroaniline (2·5 g.) in ethanol (50 ml.) when shaken with Pd in hydrogen absorbed the theoretical amount of gas in 150 min.

27. *p*-Nitroaniline under the same conditions as the *o*-isomer gave only unchanged material.

28. *o*-Nitroacetanilide (2·5 g.), CH (14 g.), ethanol (10 ml.), and Pd (15 mg.) after 17 hr. gave *o*-aminoacetanilide (2·05 g.), m. p. 132—133° (Bell and Kenyon, *J.*, 1926, 954 give m. p. 132°).

29. *m*-Nitroacetanilide (2·5 g.), CH (14 ml.), and Pd (15 mg.) after 17 hr. gave *m*-aminoacetanilide as the hydrochloride (2·08 g.), m. p. 246° (free base m. p. 86°; Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1917, **39**, 1448, give m. p. 87°).

30. *p*-Nitroacetanilide (2·5 g.), CH (14 g.), ethanol (10 ml.), and Pd (15 mg.) after 48 hr. yielded unchanged nitro-compound (1·75 g., 70% recovery) and *p*-aminoacetanilide, m. p. 161°.

31. *NN*-Dimethyl-*m*-nitroaniline (2·07 g.; Groll, *Ber.*, 1886, **19**, 198), CH (14 g.), and Pd (20 mg.) after 17 hr. gave *NN*-dimethyl-*m*-phenylenediamine (1·10 g., 73%), b. p. 152—154°/44 mm. (benzoyl derivative, m. p. 163°; Jaubert, *Bull. Soc. chim.*, 1899, **21**, 20, gives m. p. 163—164°).

32. *p*-Bromonitrobenzene (2·5 g.), CH (14 g.), and Pd (26 mg.) after 17 hr. gave no precipitate with hydrogen chloride in anhydrous ether. A solution of the same sample of *p*-bromonitrobenzene (2·5 g.) in ethanol (50 ml.) when shaken with Pd (26 mg.) in hydrogen absorbed the theoretical amount of gas in 195 min., giving aniline hydrobromide, m. p. 283°.

33. 2-Nitrothiophen (1·2 g.), CH (14 g.), and Pd (20 mg.) after 90 hr. gave no precipitate with hydrogen chloride in ether.

34. *o*-Dinitrobenzene (2 g.; Hodgson, Heyworth, and Ward, *J.*, 1948, 1512), CH (9 g.), ethanol (20 ml.), and Pd (50 mg.) after 5 hr. gave an unidentified hydrochloride (0·85 g.), m. p. 130° (Found: C, 44·6; H, 4·4; N, 17·3; Cl, 15·75%).

35. *m*-Dinitrobenzene (2·5 g.), CH (7·3 g.), palladium black (50 mg.), and tetrahydrofuran (25 ml.) after refluxing for 17 hr. gave *m*-nitroaniline as the hydrochloride (2·1 g., 82%). The base was liberated and had m. p. and mixed m. p. 112°.

36. *p*-Dinitrobenzene (2·1 g.; Hodgson *et al.*, *loc. cit.*), CH (9 g.), tetrahydrofuran (20 ml.), and Pd (20 mg.) after 19 hr. gave only unchanged dinitrobenzene.

37. 2 : 4-Dinitrotoluene (2·5 g.), CH (14 g.), and Pd (15 mg.) after refluxing for 40 hr. gave a hydrochloride (2·55 g.) from which an impure base, m. p. 68—72°, was liberted by ammonia. This was converted into 2 : 4-diaminotoluene dibenzenesulphonate (2·2 g., 75%), m. p. 195°.

38. 1-*tert.*-Butyl-2 : 4-dinitrobenzene (5 g.; Du Toit and Malherbe, *Ber.*, 1919, **52**, 321), CH (23 g.), and Pd (100 mg.) after 36 hr. gave 1-*tert.*-butyl-2 : 4-diaminobenzene as the *dihydrochloride* (4·95 g.) (Found: Cl, 30·65. $C_{10}H_{18}N_2Cl_2$ requires Cl, 30·8%). The *dibenzoyl* derivative crystallised from aqueous ethanol in plates, m. p. 259° (Found: C, 77·2; H, 6·5; N, 7·7. $C_{24}H_{24}O_2N_2$ requires C, 77·4; H, 6·5; N, 7·5%).

39. 1 : 8-Dinitronaphthalene (2·5 g.), CH (14 g.), and 10% palladised charcoal (120 mg.) after 17 hr. gave 1 : 8-diaminonaphthalene as the dihydrochloride (2·55 g.) (free base, m. p. 64°; Krollpfeiffer, *Annalen*, 1923, **430**, 199, gives m. p. 66·5°).

40. 2 : 4-Dinitrophenol (2·5 g.), CH (10 g.), ethanol (20 ml.), and 5% palladised charcoal (250 mg.) after 40 hr. gave 2 : 4-diaminophenol as the dihydrochloride (1·71 g.), m. p. 205° (tribenzoyl derivative, m. p. 230°; Meldola and Hollely, *J.*, 1912, 912, give m. p. 240°), and an ether-insoluble product (0·20 g.) (Found: C, 61·8; H, 5·6; N, 11·05%).

41. 3 : 5-Dinitrobenzoic acid (2·5 g.), CH (14 g.), ethanol (20 mg.), and Pd (12 mg.) after 17 hr. gave 3-amino-5-nitrobenzoic acid as the hydrochloride (1·48 g.) (free base, m. p. 208°; Hüber, *Annalen*, 1883, **222**, 81, gives m. p. 208°).

42. 1 : 3 : 5-Trinitrobenzene (4·26 g.), CH (14 g.), and Pd (21 mg.) after 120 hr. gave unchanged material (3·4 g., 80%) and 3 : 5-dinitroaniline (0·34 g.), m. p. 157°.

43. 2 : 4 : 6-Trinitrotoluene (3 g.), CH (10 ml.), ethanol (20 ml.), and Pd (20 mg.) after 41 hr. gave a mixture which was extracted with 6N-hydrochloric acid (15 ml.). On dilution with water, 4-amino-2 : 6-dinitrotoluene (0·33 g.), m. p. 168° (Brady, Day, and Reynolds, *J.*, 1929, 2264, give m. p. 171°), was precipitated. On addition of ammonia to the filtrate until the pH was 9, 2-amino-4 : 6-dinitrotoluene (0·27 g.), m. p. 155° (McGookin, Swift, and Tittensor, *J. Soc. Chem. Ind.*, 1940, **59**, 92, give m. p. 155°), was precipitated.

44. Picric acid (2·5 g.), CH (8 g.), tetrahydrofuran (25 ml.), and Pd (50 mg.) after 13 hr. gave picramic acid as the hydrochloride (0·67 g.) [free base m. p. 169°; *N*-acetyl derivative, m. p. 204° (Pear and Dehn, *J. Amer. Chem. Soc.*, 1938, **60**, 925 give 204—205°)].

Transfer-hydrogenation of Nitrosobenzene and Phenylhydroxylamine.—(*a*) Nitrosobenzene (2·5 g.), *cyclo*hexene (15 ml.), and Pd (25 mg.) were heated under reflux. The colour of the solution changed from green to dark-brown within a few minutes. After 7 hr., the catalyst was filtered off and the lower-boiling constituents were removed by distillation on the steam-bath. The dark, tarry residue was dissolved in ether and anhydrous hydrogen chloride was passed in. No aniline hydrochloride was obtained. (*b*) Phenylhydroxylamine (1·5 g.), *cyclo*hexene (20 ml.), and Pd (15 mg.) were heated under reflux for 7 hr. Working up as above gave aniline hydrochloride (0·30 g., 17%), m. p. 196°. A similar experiment in which reflux was continued for 17 hr. gave a 30% yield (0·34 g.) of aniline hydrochloride.

Effects of m-*Nitroaniline and* m-*Phenylenediamine on Disproportionation and Transfer.*—(a) *cyclo*Hexene (0·6 g.), ethanol (75 ml.), and 10% palladised charcoal (100 mg.) were heated under reflux. After 1 hr., the catalyst was filtered off and the solution distilled. The distillate had $\lambda_{max.}$ 2550, $E^{1\%}_{1\,cm.}$ 0·0375, corresponding to $1·33 \times 10^{-3}$ mole of benzene. In a parallel experiment, in which *m*-nitroaniline (50 mg.) was added and the solution was distilled through a short column before spectrometric assay, $0·45 \times 10^{-3}$ mole of benzene was formed. (b) *cyclo*Hexene (0·6 g.), ethanol (50 ml.), and 10% palladised charcoal (150 mg.) were heated under reflux. After 1 hr., the distillate exhibited $\lambda_{max.}$ 2550, $E^{1\%}_{1\,cm.}$ 0·071, corresponding to $1·67 \times 10^{-3}$ mole of benzene. In a similar experiment in which freshly distilled *m*-phenylenediamine (50 mg.) was added, $0·47 \times 10^{-3}$ mole of benzene was formed.

Rate Measurements.—Preliminary rate-measurements on the transfer hydrogenation of *p*-nitrotoluene by *cyclo*hexene were carried out by the following technique which will be described in more detail later. A catalyst foil, consisting of a platinum foil (1″ × 1″) coated electrolytically with a thin film of palladium (cf. Nylen, *Z. Elektrochem.*, 1937, **43**, 921; Hamer and Acree, *J. Res. Nat. Bur. Stand.*, 1944, **33**, 87), was mounted on the end of a glass stirrer and placed inside the bulb of a reaction vessel of the type described by Braude, Jones, and Stern (*J.*, 1946, 396); it was provided with a small, glass-stoppered side-arm. The glass stirrer passed through the central neck of the flask by means of a liquid seal filled with solvent and was attached to a synchronous motor. A solution of *p*-nitrotoluene (0·25 g.) and *cyclo*hexene (1 g.) in ethanol or methanol (50 ml.) was placed in the flask contained in a thermostatted bath. As soon as thermal equilibrium was attained, the stirrer carrying the catalyst foil was introduced and rotated at 470 r.p.m. At suitable intervals, 1-ml. samples of the solution were withdrawn through the stoppered side-arm by means of a long-stem, graduated pipette and immediately diluted with 9 ml. of ethanol. The concentration (*c*) of *p*-nitrotoluene was then determined by measuring the extinction at 3650 Å in a 1-cm. cell. *p*-Nitrotoluene and *p*-toluidine exhibit

$E^{1\%}_{1\ cm.}$ 10·4 and 0·04, respectively, at this wave-length. Details of four typical runs carried out with the same foil are given below (cf. Fig. 1).

(*a*) In ethanol at 55·7° :

Time, min.	0	30	60	90	160	215
E	0·465	0·415	0·398	0·395	0·383	0·384
c, mole/l.	1·63	1·46	1·40	1·39	1·34	1·35

(*b*) In methanol at 64° :

Time, min.	0	270	1080
E	0·462	0·165	0·012
c, mole/l.	1·63	0·58	0·04

(*c*) In ethanol at 78° :

Time, min.	0	10	20	30	40	55	85	115	265
E	0·469	0·435	0·411	0·392	0·365	0·354	0·293	0·258	0·138
c, mole/l.	1·64	1·52	1·44	1·38	1·24	1·20	1·03	0·905	0·484

(*d*) In ethanol at 78° :

Time, min.	0	15	30	45	90	135	180	240	360
E	0·467	0·450	0·432	0·407	0·370	0·310	0·290	0·247	0·233
c, mole/l.	1·64	1·58	1·52	1·43	1·30	1·09	1·02	0·868	0·782

These results clearly illustrate the pronounced influence of ebullition [runs (*a*) and (*b*)], the low temperature-coefficient of the reaction [runs (*b*) and (*c*)], and the slow " ageing " of the catalyst [runs (*c*) and (*d*)].

Grateful acknowledgment is made to the Kent Education Committee and the Department of Scientific and Industrial Research for a Maintenance Grant (K. R. H. W.).

Organic Chemistry Department,
Imperial College of Science and Technology,
South Kensington, London, S.W.7. [*Received, February 24th,* 1954.]

Hydrogen Transfer. Part VIII. Metal-catalysed Transfer-hydrogenation of Miscellaneous Acceptors.*

By E. A. Braude, R. P. Linstead, P. W. D. Mitchell, and K. R. H. Wooldridge.

[Reprint Order No. 5159.]

The palladium-catalysed transfer-hydrogenation of miscellaneous acceptors by *cyclo*hexene has been investigated. Not only ethylenic, acetylenic, and nitro-groups (Parts VI and VII), but also azomethine, azo-, and azoxy-groups, and some halogen compounds undergo reduction or hydrogenolysis, whereas cyano- and carbonyl groups (except in quinones and α-diketones) do not react.

In addition to that of ethylenic, acetylenic and nitro-compounds (Parts VI and VII *), the transfer-hydrogenation of a number of other types of acceptors by *cyclo*hexene in the presence of palladium has been examined.

Benzylideneaniline, azobenzene, and azoxybenzene readily underwent hydrogenolysis to aniline, and 2 : 2′-dimethoxyazoxybenzene similarly gave *o*-anisidine. In the case of azobenzene, the intermediate product, hydrazobenzene, could be isolated if the reaction was interrupted at an early stage. Thus C=N and N=N bonds exhibit a reactivity similar to that of C=C, as in direct catalytic hydrogenation (cf. Adkins and Shriner in Gilman, " Organic Chemistry " Chapter 9, Wiley, New York, 1943). On the other hand, the cyano-group in benzonitrile, as in nitrobenzonitriles, was not reduced. The C=N bond is also more resistant than C=C to direct catalytic hydrogenation.

The carbonyl group in aldehydes and ketones, *e.g.*, butyraldehyde, benzaldehyde, *cyclo*hexanone, acetophenone, and benzophenone, was not reduced by *cyclo*hexene and

* Parts VI and VII, preceding papers.

palladium under the usual conditions, in accord with the observations made with substituted nitro-compounds. Moreover, in αβ-ethylenic aldehydes and ketones, *e.g.*, crotonaldehyde, cinnamaldehyde and mesityl oxide, the ethylenic bond is also unreactive, in contrast to the behaviour of ethylenic acids (Part VI). On the other hand, benzil is slowly converted into benzoin, and benzoquinone into quinol, in conformity with the fact that α-diketones and quinones generally have reduction potentials appreciably different from those of other carbonyl compounds (cf. Cox and Adkins, *J. Amer. Chem. Soc.*, 1938, **60**, 1151; 1939, **61**, 3364). With benzoquinone, slow uncatalysed hydrogen transfer also takes place (Parts II and III, *J.*, 1954, 3548, 3564) and it is of interest that, whereas transfer from thermally unreactive donors (*e.g.*, *cyclo*hexene, 1 : 2-dihydrobenzene, 1 : 2-dihydronaphthalene) shows appreciable metal catalysis, transfer from thermally reactive donors (*e.g.*, 1 : 4-dihydrobenzene, 1 : 4-dihydronaphthalene, and 1 : 4-dihydrophthalic acid) is only slightly accelerated by palladium. In these cases, the heterogeneously catalysed reaction evidently does not compete effectively with the homogeneous one.

Semiquantitative rate measurements on the effects of potential acceptors on the disproportionation of *cyclo*hexene show that the failure of aldehydes and ketones to undergo transfer is not always due to the same cause (cf. Part VI). Benzaldehyde and *m*-nitrobenzaldehyde almost completely inhibit the disproportionation and are evidently adsorbed strongly, whereas mesityl oxide has little effect on the rate of disproportionation and is presumably adsorbed very weakly.

Benzyl chloride was converted into toluene by boiling *cyclo*hexene and palladium, and cinnamyl chloride similarly underwent hydrogenolysis accompanied by reduction of the double bond to give propylbenzene. Benzoyl chloride reacted slowly to give a low yield of benzaldehyde.

Experimental.

Pd refers to palladium black prepared by the method of Wieland (*Ber.*, 1912, **45**, 484). Pd–C refers to 10% palladised charcoal prepared by the method of Linstead and Thomas (*J.*, 1940, 1130).

Benzylideneaniline and cyclo*Hexene.*—Acceptor (2·5 g.), donor (1·3 ml.), Pd (100 mg.), and tetrahydrofuran (50 ml.) were refluxed for 24 hr. The catalyst was filtered off, the solvent evaporated, and the residue extracted with 2N-hydrochloric acid. The extract was made alkaline with sodium hydroxide and extracted with ether. On passage of anhydrous hydrogen chloride into the dried ethereal solution, aniline hydrochloride (0·74 g., 44%), m. p. 196°, was precipitated.

Azobenzene and cyclo*Hexene.*—(*a*) Acceptor (5 g.), donor (2·8 ml.), Pd (100 mg.), and tetrahydrofuran (50 ml.) were refluxed for 15 hr. The product was worked up by Andrews and Lowry's procedure (*J. Amer. Chem. Soc.*, 1934, **56**, 1411), giving hydrazobenzene (converted into benzidine sulphate, 0·25 g., 3%) and aniline hydrochloride (0·25 g., 7%). (*b*) Acceptor (2·5 g.), donor (10 ml.), Pd–C (200 mg.), and ethanol (50 ml.) were refluxed until the solution was colourless (23 hr.). Working up as above gave only aniline hydrochloride (2·47 g., 97%).

Azoxybenzene and cyclo*Hexene.*—Acceptor (2·5 g.), donor (10 ml.), Pd–C (250 mg.), and ethanol (50 ml.) were refluxed for 46 hr. Working up gave aniline hydrochloride (0·38 g., 8%).

2 : 2′-*Dimethoxyazoxybenzene and* cyclo*Hexene.*—Carried out exactly as the preceding experiment, this gave *o*-anisidine (2·0 g., 84%), b. p. 59—60°/1 mm., after 4 hours' refluxing.

Benzonitrile and cyclo*Hexene.*—The nitrile (5 g.), *cyclo*hexene (8 ml.), Pd (100 mg.), and tetrahydrofuran (50 ml.) were refluxed for 28 hr. Working up for benzylamine gave less than 10 mg. of hydrochloride.

Aldehydes and Ketones, and cyclo*Hexene.*—The following were recovered unchanged (< 90%) when 0·01 mole was refluxed with Pd (50 mg.), *cyclo*hexene (3·3 g.), and tetrahydrofuran (25 ml.) for the periods stated : butyraldehyde (25 hr.), benzaldehyde (23 hr.), crotonaldehyde (91 hr.), cinnamaldehyde (47 hr.), *cyclo*hexanone (92 hr.), benzophenone (65 hr.) and mesityl oxide (42 hr.).

Benzoquinone and cyclo*Hexene.*—(*a*) The quinone (1·3 g.), Pd (50 mg.), *cyclo*hexene (0·5 g.), and tetrahydrofuran (30 ml.) were refluxed for 40 hr. After removal of the catalyst and solvent, the residue was dissolved in hot benzene (15 ml.). On cooling, quinhydrone (0·35 g.), m. p. 170°, separated. (*b*) A similar experiment in which palladium was omitted gave 0·06 g. of quinhydrone after 5 days' refluxing.

Benzil and cyclo*Hexene.*—Benzil (2·1 g.), Pd (50 mg.), *cyclo*hexene (1·64 g.), and tetrahydro-

furan (25 ml.) were refluxed for 40 hr. Removal of the catalyst and solvent gave a product, m. p. 73—91°, 0·5 g. of which gave 0·156 g. of cuprous oxide on boiling with Fehling's solution, corresponding to a benzoin content of 45%. The presence of benzoin was confirmed by the formation of the acetate, m. p. and mixed m. p. 81—83°, and the phenylurethane, m. p. and mixed m. p. 166—168°.

Benzoquinone and 1 : 2-*Dihydrobenzene.*—(*a*) The quinone (1·34 g.), 1 : 2-dihydrobenzene (0·5 g., b. p. 82°/752 mm., n_D^{20} 1·4695; prepared by Crossley's method, *J.*, 1904, **85**, 1416), Pd (50 mg.), and tetrahydrofuran (25 ml.) were refluxed for 40 hr. The solvent and catalyst were removed, and the dark-green product was crystallised from benzene, giving quinhydrone (0·95 g.), m. p. 168—170°.

(*b*) The above experiment was repeated but without the palladium. The orange product, which consisted largely of the quinone–diene adduct (cf. Diels, Alder, and Stein, *Ber.*, 1929, **62**, 2364), was extracted with *cyclo*hexane and the residue was dissolved in benzene containing some benzoquinone. On cooling, a small amount of quinhydrone (40 mg.) separated.

Benzoquinone and 1 : 4-*Dihydrobenzene.*—(*a*) The quinone (1·34 g.), 1 : 4-dihydrobenzene (0·5 g.; b. p. 86°, n_D^{15} 1·4795; prepared by Wibaut and Haak's method, *Rec. Trav. chim.*, 1948, **67**, 85), palladium (50 mg.), and tetrahydrofuran (25 ml.) were refluxed for 40 hr. The solid product obtained on evaporation was dissolved in hot benzene; on cooling, quinhydrone (1·0 g.), m. p. 169°, separated. (*b*) A similar experiment, but without palladium, gave 0·9 g. of quinhydrone.

Benzoquinone and 1 : 2-*Dihydronaphthalene.*—(*a*) The quinone (1·67 g.), 1 : 2-dihydronaphthalene (1·0 g.), Pd (50 mg.), and tetrahydrofuran (25 ml.) were refluxed for 168 hr. The solid product was extracted with boiling *cyclo*hexane (20 ml.). The residue was quinhydrone (0·63 g.). The *cyclo*hexane solution on partial evaporation yielded benzoquinone (0·35 g.). The remaining solvent was then distilled off and the residue was treated with picric acid in ethanol, giving naphthalene picrate (0·61 g.), m. p. and mixed m. p. 146—148°. (*b*) A similar experiment, but without palladium, gave only 0·1 g. of quinhydrone and no picrate could be obtained from the *cyclo*hexane-soluble residue.

Benzoquinone and 1 : 4-*Dihydronaphthalene.*—The reactions were carried out exactly as with 1 : 2-dihydronaphthalene, except that the time of reflux was 24 hr. (*a*) In the presence of palladium, the products isolated were quinhydrone (0·44 g.), unchanged benzoquinone (0·50 g.), and naphthalene, as the picrate (0·73 g.). (*b*) In the absence of palladium, there were obtained quinhydrone (0·35 g.), benzoquinone (0·62 g.), and naphthalene picrate (0·60 g.).

Benzoquinone and 1 : 4-*Dihydrophthalic Acid.*—(*a*) Benzoquinone (1·3 g.), the acid (1·0 g.; m. p. 145°; prepared according to Alder and Backendorf, *Ber.*, 1938, **71**, 2199), palladium (50 mg.), and tetrahydrofuran (25 ml.) were refluxed for 120 hr. The catalyst and solvent were removed and the solid products were extracted with boiling benzene. The residue, on crystallisation from water, gave phthalic acid (0·30 g.), m. p. and mixed m. p. 195° (*p*-nitrobenzyl ester, m. p. 155°). The benzene solution was evaporated and the residue partitioned between ether and aqueous sodium hydrogen carbonate. From the ether layer, quinhydrone (0·68 g.) was obtained, while the aqueous layer, on acidification, gave unchanged dihydrophthalic acid (0·20 g.), m. p. 145°. (*b*) A similar experiment, but without palladium, gave phthalic acid (0·28 g.), quinhydrone (0·53 g.), and unchanged dihydrophthalic acid (0·22 g.).

Benzoquinone and 9 : 10-*Dihydroanthracene.*—(*a*) The quinone (1·2 g.), 9 : 10-dihydroanthracene (1·0 g.), m. p. 108°, palladium (50 mg.), and tetrahydrofuran (25 ml.) were refluxed for 120 hr. After removal of the catalyst and solvent, the solid product was extracted with boiling *cyclo*hexane and then with water. Treatment of the aqueous solution with charcoal and evaporation gave quinol (0·45 g.), m. p. and mixed m. p. 172°. The water-insoluble residue was crystallised from benzene–ethanol and gave anthracene–benzoquinone adduct (0·13 g.) (cf. Clar, *Ber.*, 1931, **64**, 1684; Bartlett, Ryan, and Cohen, *J. Amer. Chem. Soc.*, 1942, **64**, 2649) (Found: C, 84·1; H, 5·0. Calc. for $C_{20}H_{14}O_2$: C, 83·9; H, 4·9%). (*b*) A similar experiment, without palladium, gave 0·11 g. of quinol and 0·04 g. of adduct.

Benzyl Chloride and cyclo*Hexene.*—The chloride (5·0 g.), *cyclo*hexene (15 ml.), and Pd (100 mg.) were refluxed for 30 hr. with exclusion of moisture. Hydrogen chloride was steadily evolved. On fractionation, a mixture of benzene and toluene was obtained which was treated with boiling 0·25N-sodium carbonate (100 ml.) and potassium permanganate (12 g.). The solution was decolourised with sodium sulphite, filtered, concentrated, acidified, and cooled, giving benzoic acid (2·35 g., 49%), m. p. 123°.

Cinnamyl Chloride and cyclo*Hexene.*—The chloride (2·7 g.), *cyclo*hexene (15 ml.), and Pd (100 mg.) were refluxed for 40 hr. Fractionation of the product gave *n*-propylbenzene (1·0 g.,

50%), b. p. 160°, n_D^{19} 1·4920 (von Auwers and Kolligs, *Ber.*, 1922, **55**, 26, give b. p. 159·5°, n_D^{20} 1·4924).

Benzoyl Chloride and cyclo*Hexene*.—The chloride (2 g.), *cyclo*hexene (15 ml.), and Pd (50 mg.) were refluxed for 16 hr. The catalyst was filtered off and the solution heated with methanol for 1 hr. to remove unchanged chloride. The solvents were then removed on the steam-bath and the residual liquid treated with Brady's reagent, giving benzaldehyde 2 : 4-dinitrophenylhydrazone (0·35 g., 10%), m. p. and mixed m. p. 136°. No benzaldehyde was obtained in a similar experiment in which Pd was omitted.

Rate Measurements.—These were carried out by the procedure described in Part VI. The following runs refer to 1M-solutions of *cyclo*hexene in boiling tetrahydrofuran (25 ml.) containing 50 mg. of Pd. x is the volume (ml.) of 0·05M-bromine consumed by 1 ml. after t hours.

(i) *cyclo*Hexene alone :

t	0	0·5	1	1·5	3	4·5	10
x	19·7	12·8	8·4	6·4	3·2	1·2	0·3

(ii) With mesityl oxide (0·5M) :

t	0	1	5	12	21	50	74	147
x	29·5	19·6	12·2	10·0	9·5	8·9	9·0	8·9

(iii) With benzaldehyde (0·5M) :

t	0	1	3	20	44	68
x	20·0	18·9	18·4	18·2	17·9	16·8

(iv) With *m*-nitrobenzaldehyde (0·5M) :

t	0	1	4	10	22	82
x	19·5	19·8	19·4	19·7	20·0	20·1

ORGANIC CHEMISTRY DEPARTMENT,
IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
SOUTH KENSINGTON, LONDON, S.W.7.

[*Received, February 24th*, 1954.]

Organometallic and Organometalloidal Fluorine Compounds. Part X. Trifluoromethyl-phosphonous and -phosphonic Acids.†*

By F. W. BENNETT, H. J. EMELÉUS, and R. N. HASZELDINE.

[Reprint Order No. 5216.]

Oxidative hydrolysis of the compounds $CF_3 \cdot PX_2$ or $(CF_3)_2PX$ (X = Cl or I), or controlled hydrolysis of $(CF_3)_3P$ followed by oxidation, yields trifluoromethylphosphonic acid, $CF_3 \cdot PO(OH)_2$. This is a dibasic acid ($K_1 = 6{\cdot}8 \times 10^{-2}$, $K_2 = 1{\cdot}2 \times 10^{-4}$) and is one of the strongest known acids of phosphorus. Salts have been prepared, and their infra-red spectra are discussed.

Trifluoromethylphosphonous acid, $CF_3 \cdot P(OH)_2$, differs considerably from the phosphonic acid, since it is volatile in water vapour at low pressure, is monobasic, and yields fluoroform when its aqueous solutions are heated or treated with alkali. It has been isolated as its monosodium salt, and spectroscopic evidence shows this to be $CF_3 \cdot PH(:O)(ONa)$ rather than $CF_3 \cdot P(OH)(ONa)$. Solutions of the acid are obtained by the aqueous hydrolysis of the compounds $CF_3 \cdot PX_2$ or $(CF_3)_2PX$ or by the controlled stepwise hydrolysis of $(CF_3)_3P$. Oxidation yields trifluoromethylphosphonic acid. Bistrifluoromethylphosphinous acid, $(CF_3)_2P \cdot OH$, is unstable in water and yields trifluoromethylphosphonous acid and fluoroform.

THIS paper, which records the beginning of a systematic investigation of perfluoroalkyl acids containing phosphorus, is concerned with the synthesis and properties of trifluoromethyl-phosphonous and -phosphonic acids [(I) and (II)]. Trifluoromethylphosphine oxide (III), a third possible acid containing only one trifluoromethyl group, has yet to be

* Part IX, *J.*, 1954, 881, erroneously numbered Part VIII; Part VIII, *J.*, 1953, 2372.
† Presented at Amer. Chem. Soc. Meeting, Chicago, September, 1953.

investigated. The forms containing four-co-ordinated phosphorus are more probable than those containing tervalent phosphorus.

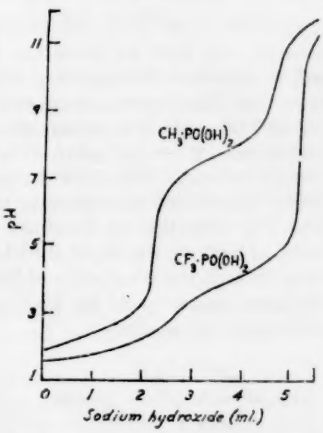
$$CF_3{\cdot}P(OH)_2 \rightleftharpoons CF_3{\cdot}PH(:O){\cdot}OH \qquad CF_3{\cdot}PO(OH)_2 \qquad CF_3{\cdot}PH_2(:O) \rightleftharpoons CF_3{\cdot}PH(OH)$$
$$\text{(I)} \qquad\qquad \text{(II)} \qquad\qquad \text{(III)}$$

Aqueous hydrolysis of chlorobistrifluoromethylphosphine or dichlorotrifluoromethylphosphine or the corresponding iodo-compounds (Part VII; *J.*, 1953, 1565) gives a solution which, on treatment with hydrogen peroxide followed by evaporation to dryness, yields trifluoromethylphosphonic acid. The oxidative hydrolysis is performed in two stages because of the vigour of the direct oxidation of the halogeno-compounds with hydrogen peroxide:

$$(CF_3)_2PX \xrightarrow{H_2O\text{–}H_2O_2} \text{(II)} + CHF_3 + HX$$
$$CF_3{\cdot}PX_2 \xrightarrow{H_2O\text{–}H_2O_2} \text{(II)} + 2HX$$

The phosphonic acid is also obtained by oxidation of trifluoromethylphosphine, $CF_3{\cdot}PH_2$.

Trifluoromethylphosphonic acid is dibasic with $K_1 = 6{\cdot}8 \pm 1{\cdot}2 \times 10^{-2}$, $K_2 = 1{\cdot}2 \pm 0{\cdot}1 \times 10^{-4}$, corresponding to values for pK_1 and pK_2 of $1{\cdot}16 \pm 0{\cdot}1$ and $3{\cdot}93 \pm 0{\cdot}03$, respectively. In aqueous solution the acid approximates in strength to dichloroacetic acid, but the slightness of the first inflection point in the titration curve (see Figure) indicates the relatively small ratio of the two dissociation constants (*ca.* 575); in this respect it resembles oxalic and malonic acid. The titration curve for the much weaker methylphosphonic acid ($K_1 = 3{\cdot}3 \times 10^{-3}$, $K_2 = 4{\cdot}6 \times 10^{-8}$) is also shown in the Figure; its shape is typical of those of most dibasic acids, and the K_1/K_2 ratio is $7{\cdot}25 \times 10^4$.



Comparison of the pK values shown in the annexed Table reveals the marked electrophilic nature of the trifluoromethyl group. Trifluoromethylphosphonic acid is, in fact, one of the strongest known phosphorus acids. The pK_2 values for phosphoramidic acid, $H_2N{\cdot}PO(OH)_2$, and aminomethylphosphonic acid, $H_2N{\cdot}CH_2{\cdot}PO(OH)_2$ (3·8 and 5·9, respectively; Rumpf and Chavanne, *loc. cit.*), approach fairly closely the value for trifluoromethylphosphonic acid.

The last acid yields ammonium, barium, and mono- and di-sodium salts. The sparingly soluble barium salt crystallises with 1·5 molecules of water. Since solutions of the acid or its salts fail to give a precipitate with solutions of lead acetate, silver nitrate, mercurous nitrate, or calcium chloride, the corresponding salts are probably soluble. That the same

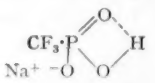
	pK_1	pK_2
Pyrophosphoric acid, $H_4P_2O_7$	0·85	—
Trifluoromethylphosphonic acid (II)	1·16	3·93
Phosphorous acid, H_3PO_3	1·41 [1]	6·7 [1]
Methyl dihydrogen phosphate, $MeO{\cdot}PO(OH)_2$	1·54 [2]	6·31 [2]
Ethyl dihydrogen phosphate, $EtO{\cdot}PO(OH)_2$	1·60 [2]	6·62 [2]
Trichloromethylphosphonic acid, $CCl_3{\cdot}PO(OH)_2$	1·63 [3]	4·81 [3]
Phosphoric acid, H_3PO_4	1·97 [2]	6·82 [2]
Phenylphosphonic acid, $Ph{\cdot}PO(OH)_2$	2·2 [4]	—
Methylphosphonic acid, $Me{\cdot}PO(OH)_2$	2·48	7·34
Ethylphosphonic acid, $Et{\cdot}PO(OH)_2$	2·45 [5]	7·85 [5]

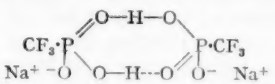
[1] Yost and Russell, "Systematic Inorganic Chemistry," Prentice Hall, New York, 1944. [2] Kumler and Eiler, *J. Amer. Chem. Soc.*, 1943, **65**, 2355. [3] Crofts and Kosolapoff, *ibid.*, 1953, **75**, 5738. [4] Topley, *Chem. and Ind.*, 1950, S 859. [5] Rumpf and Chavanne, *Compt. rend.*, 1947, **224**, 919.

trifluoromethyl acid of phosphorus is obtained by each of the routes described above is shown by comparison of the infra-red spectra of the mono- and di-sodium salts prepared in each case.

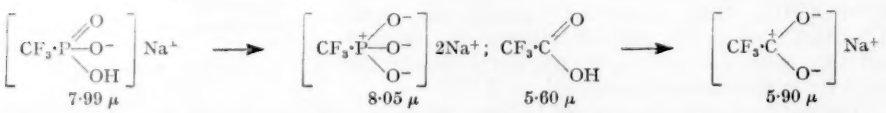
The infra-red spectra of mono- and di-sodium trifluoromethylphosphonates (C.S. Nos. 125 and 126 *) are suitable for characterisation of the acid. The spectrum of the monosodium salt shows no free hydroxyl vibration near 2·76 μ; instead, a broad weak band appears at 4·25 μ and this is assigned to the hydrogen-bonded P–OH group. This vibration is at a much longer wave-length than the bonded P–OH vibration (3·70—3·80 μ) in other phosphonic acids (*e.g.*, phenylphosphonic acid 3·72 μ, Daasch and Smith, *loc. cit.*; *cyclo*hexylphosphonic acid 3·75 μ, Bellamy and Beecher, *J.*, 1952, 1701), and the very strong hydrogen bonding of type (IV) or (V) so revealed is consistent with the strength of trifluoromethylphosphonic acid. The disodium salt shows no band in the 3·5—5 μ region, thus confirming the assignment for the P–OH vibration.

The presence of the electronegative trifluoromethyl group on the phosphorus atom of monosodium trifluoromethylphosphonate would be expected to cause a shift of the P:O (*i.e.*, $P^+–O^-$) vibration to wave-lengths shorter than those (7·9—8·5 μ) for the corresponding vibration in aliphatic or aromatic phosphonic acids, just as the C:O vibration in aldehydes, acids, esters, ketones, etc., is shifted to shorter wave-lengths when fluorine is present in the molecule (Haszeldine, *Nature*, 1951, **168**, 1028). On the other hand, the strong hydrogen

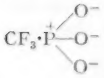
(IV) 

 (V)

bonding will tend to move the P:O vibration to longer wave-lengths, although this shift will be less than the opposing shift caused by the inductive effect. These predictions are borne out, since monosodium trifluoromethylphosphonate shows a strong band in the infra-red at 7·99 μ which is outside the 8·2—8·8 μ region for the strong carbon–fluorine stretching vibrations; these are centred on 8·34 μ. The P:O vibration is thus near to that in phosphoryl chloride (7·81 μ) or dialkyl phosphites (7·70—8·00 μ) (Meyrick and Thompson, *J.*, 1950, 225) which also contain electronegative atoms or groups attached to phosphorus. The P:O vibration in disodium trifluoromethylphosphonate is clearly the strong sharp band at 8·05 μ; the slight shift to longer wave-length compared with the monosodium salt, even though the possibility of hydrogen bonding is now removed, is caused by increase in the ionic character of the P:O bond, analogous to the shift of the C:O band in salts of carboxylic acids, thus:



The P–OH deformation vibration in the spectrum of monosodium trifluoromethylphosphonate is assigned to the strong 10·64 μ band; this disappears in the spectrum of the disodium salt, and is replaced by a strong band at 10·22 μ which is probably characteristic of the system shown inset. The band at 13·5 or 13·6 μ in the spectra is caused by a trifluoromethyl deformation vibration (see Part VII, *loc. cit.*).



The aqueous hydrolysis of chloro- and iodo-bistrifluoromethylphosphines, and of dichlorotrifluoromethylphosphine, yields trifluoromethylphosphonous acid (I). Di-iodotrifluoromethylphosphine also yields (I), but there is evidence that in this case other products result as the conditions and proportion of reactants are varied. Trifluoromethylphosphonous acid has not been isolated as the free acid, since it is volatile in water vapour at reduced pressure. It behaves as a strong monobasic acid, and differs sharply from trifluoromethylphosphonic acid, since it liberates fluoroform quantitatively at pH >11 or when its solutions are heated at 100°. The monosodium salt is obtained by the controlled hydrolysis of tristrifluoromethylphosphine, iodobistrifluoromethylphosphine, or di-iodotrifluoromethylphosphine with dilute aqueous sodium hydroxide. Sodium trifluoromethyl-

* Spectra thus designated have been deposited with the Society. Photocopies may be obtained, price 3*s.* 0*d.* each by application to the General Secretary, quoting the C.S. No.

phosphonite, which can be isolated as a white solid, yields fluoroform when treated with an excess of aqueous alkali. Treatment of the salt with sulphuric acid yields a solution of trifluoromethylphosphonous acid which is freed from sodium sulphate and excess of sulphuric acid by distillation under reduced pressure.

The infra-red spectrum of sodium trifluoromethylphosphonite (C.S. No. 127) shows C–F absorption at 8·80, 9·00, and 9·25 μ, and a CF_3 deformation at 13·6 μ. There is also a band at 4·2 μ which is much sharper than a P–OH vibration, and is more plausibly assigned to a P–H stretching vibration. Sodium trifluoromethylphosphonite is thus better represented as $CF_3{\cdot}PH(:O)(ONa)$ than as $CF_3{\cdot}P(OH)(ONa)$. This conclusion is strongly supported by the presence of a strong band at 8·05 μ, which can be assigned only to the P:O vibration, and by the fact that trifluoromethylphosphonous acid is a strong monobasic acid. It is doubtful if any alkylphosphonous acids have yet been prepared in the stable $R{\cdot}P(OH)_2$ form. Dialkyl phosphites are similarly best represented by the form $(RO)_2PH(:O)$, since their infra-red spectra show P–H absorption at 4·1 μ [*e.g.*, $(MeO)_2P{\cdot}OH$ 4·11; $(EtO)_2P{\cdot}OH$ 4·11; $(Pr^iO)_2P{\cdot}OH$ 4·11; $(Bu^nO)_2P{\cdot}OH$ 4·15], and P:O absorption at 7·94—8·00 μ; arylphosphonous acids also show P–H and P:O absorption [*e.g.*, $Ph{\cdot}P(OH)_2$ 4·20; $Ph{\cdot}P(OEt)(OH)$ 4·25 μ (Meyrick and Thompson; Daasch and Smith, *locc. cit.*)]. Trifluoromethylphosphonous acid and its sodium salt show only weak reducing properties (cf. phosphorous acid).

Oxidation of an aqueous solution of trifluoromethylphosphonous acid yields trifluoromethylphosphonic acid.

The loss of one equivalent of fluoroform during the aqueous hydrolysis of the compounds $(CF_3)_2PX$ points to the instability of bistrifluoromethylphosphinous acid which accords with the general behaviour of other substituted phosphinous acids, although the usual product is the substituted phosphine, $2R_2P{\cdot}OH \longrightarrow R_2PH + R_2PO{\cdot}OH$ (Kosolapoff, "Organo-phosphorus Compounds," Wiley, New York, 1950, p. 137). The preparation of the second possible acid containing two trifluoromethyl groups, *i.e.*, bistrifluoromethylphosphinic acid, is being investigated.

Experimental

The general techniques were similar to those described in Part VII (*loc. cit.*). Products were identified tensimetrically, by molecular-weight determination, and by infra-red spectroscopic examination whenever possible.

Trifluoromethylphosphonic Acid.—(a) *From di-iodotrifluoromethylphosphine.* The iodo-compound (2·61 g.) was kept *in vacuo* with distilled water (5 ml.) at 20° until the mixture became homogeneous (2 hr.). Water (10 ml.) was then added, followed by unstabilised hydrogen peroxide (100-vol.; 5 ml.), dropwise. The precipitated iodine was washed with water (2 ml.), and the combined solution was evaporated by freeze-drying (6 days). The light brown hygroscopic residue was heated at 85°/10^{-3} mm. to give a sublimate of *trifluoromethylphosphonic acid* (0·92 g., 83%) as white hygroscopic crystals, m. p. 81—82° (Found: F, 37·5%; equiv., 74. $CH_2O_3F_3P$ requires F, 38·0%; equiv., 75). A small amount of iodic acid remained in the sublimation apparatus. Direct addition of the oxidising agent to di-iodotrifluoromethylphosphine causes it to ignite explosively. Trifluoromethylphosphonic acid was decomposed by sodium fusion at 600° for analysis.

(b) *From iodobistrifluoromethylphosphine.* The iodo-compound (0·736 g.) had reacted completely with water (2 ml.) at 20° after 30 min. to give fluoroform (0·170 g., 49%). Hydrogen peroxide (100-vol.; 2 ml.) was then added dropwise until liberation of iodine was completed, and after filtration evaporation to dryness by freeze-drying (10 days) gave trifluoromethylphosphonic acid (0·33 g., 88%) which on vacuum-sublimation gave the pure compound (0·278 g., 74%).

(c) *From dichlorotrifluoromethylphosphine.* The reaction of this phosphine (0·692 g.) with water (0·5 ml.), followed by oxidation with hydrogen peroxide (50-vol.; 2 ml.), evaporation (5 days), and sublimation *in vacuo*, gave trifluoromethylphosphonic acid (0·49 g., 82%).

(d) *From chlorobistrifluoromethylphosphine.* The chloro-compound (0·467 g.) on treatment with water (2 ml.) evolved fluoroform (0·157 g., 49%) during 30 min. After 3 hr., water (5 ml.) and then hydrogen peroxide (50-vol.; 2 ml.) were added; freeze-drying (4 days) gave the phosphonic acid (0·283 g., 80%) which was further purified by vacuum-sublimation (0·206 g., 60%).

(e) *From trifluoromethylphosphine.* See Part XI (*J.*, in the press).

Salts of Trifluoromethylphosphonic Acid.—The disodium salt was prepared from the acid (made by each of the above methods) by titration with sodium hydroxide (phenolphthalein) and freeze-drying the product to constant weight. In a typical experiment, trifluoromethylphosphonic acid (0·230 g.) was neutralised with 0·49N-sodium hydroxide (6·305 ml.); freeze-drying (3 days) yielded the white *disodium trifluoromethylphosphonate* (0·291 g., 98%) (Found: Na, 23·7. $CO_3F_3Na_2P$ requires Na, 23·7%). The infra-red spectra of the disodium salts prepared were identical (C.S. No. 126); the weak bands at 2·9 and 6·15 μ are caused by moisture.

Reaction of trifluoromethylphosphonic acid with only one equiv. of sodium hydroxide, followed by freeze-drying, gave the monosodium salt. In a typical experiment, trifluoromethylphosphonic acid (0·168 g.) was treated with 0·49N-sodium hydroxide (2·32 ml.), and the solution freeze-dried to give the white monosodium trifluoromethylphosphonate (0·180 g., 94%). The infra-red spectra of the monosodium salts (C.S. No. 125) were also identical.

To trifluoromethylphosphonic acid (0·556 g.) was added 2·21N-ammonia solution (*ca.* 4 ml.), and the solution was evaporated to dryness first over silica gel, then over calcium oxide to give diammonium trifluoromethylphosphonate (0·635 g., 94%), m. p. 212—216° (decomp.).

Titration of the phosphonic acid (0·195 g.) against 0·342N-barium hydroxide (7·67 ml.) (phenolphthalein) gave an immediate precipitate which after 3 days was filtered off and dried *in vacuo* (0·414 g.). *Barium trifluoromethylphosphonate* is hydrated (Found: Ba, 43·6. $CF_3{\cdot}PO_3Ba,1{\cdot}5H_2O$ requires Ba, 43·7%) as shown by examination of its infra-red spectrum; one molecule of water is lost after 24 hr. at 120° *in vacuo*.

Titration of Trifluoromethylphosphonic Acid and Methylphosphonic Acid.—A Cambridge Instrument Co. portable mains pH meter, sensitive to ±0·01 pH unit, fitted with a glass electrode, was used. Trifluoromethylphosphonic acid (0·0430 g.), dissolved in water (5 ml.), was titrated with 0·1127N-sodium hydroxide with a slow stream of nitrogen passing to stir the solution. The titration curve (see Fig.) shows that complete neutralisation occurs at approximately pH 8, but the dissociation constants cannot be determined accurately from the graph; the method outlined by Britton ("Hydrogen Ions," Vol. I, Chapman and Hall, 1942, p. 197) was therefore used. The titration value for neutralisation occurs at 5·15 ml., whence the equivalent is 74 (Calc. for $CH_2O_3F_3P$: equiv., 75). The dissociation constants are $K_1 = 6{\cdot}81 \pm 1{\cdot}2 \times 10^{-2}$, $K_2 = 1{\cdot}18 \pm 0{\cdot}08 \times 10^{-4}$.

A 5-ml. aliquot portion of a solution of methylphosphonic acid (0·7533 g. in 150 ml.), similarly titrated with the alkali, gave the curve shown in the Fig. The points of inflection are at *ca.* pH 5·2 and 9·8 (titre values 2·26 and 4·65 ml.), and the equivalents of the acid are 98·5 and 47·8 (Calc. for CH_5O_3P: equivs., 96 and 48). Calculation gives $K_1 = 3{\cdot}31 \times 10^{-3}$, $K_2 = 4{\cdot}57 \times 10^{-8}$.

Trifluoromethylphosphonous Acid.—(a) *From tristrifluoromethylphosphine.* Tristrifluoromethylphosphine (0·655 g., 0·00275 mole) and sodium hydroxide (0·1146N; 24·0 ml.; 0·00275 mole) were shaken in a sealed tube for two days, giving unchanged tristrifluoromethylphosphine (0·0545 g., 8%), fluoroform (0·3508 g., 66%), and a neutral solution which, when evaporated to dryness by freeze-drying, gave a white solid. The solid (0·187 g.) was treated with two successive portions of 3N-sulphuric acid (*ca.* 3 ml.) and the liquid was partly evaporated by freeze-drying (2 days). The condensate, which contained the volatile trifluoromethylphosphonous acid, was treated with an excess of sodium hydroxide solution to give fluoroform (0·068 g., 81%) and sodium phosphite but no sodium phosphate (qualitative tests). The residual sulphuric acid solution, treated with an excess of sodium hydroxide, gave fluoroform (0·013 g., 14%), the total of which is thus 95%.

Sodium trifluoromethylphosphonite (C.S. No. 127) was prepared by reaction of a solution of trifluoromethylphosphonous acid with an equivalent of sodium hydroxide followed by evaporation to dryness *in vacuo*. Titration of a solution of the solid (0·087M; 2 ml.) against 0·113N-sodium hydroxide showed that the solution (initially pH 6) evolved fluoroform at pH 11·5 (1·29 ml. of NaOH) [Found: CF_3 (as CHF_3), 44·0. CHO_2F_3NaP requires CF_3, 44·9%].

Sodium trifluoromethylphosphonite (0·087 g.), oxidised by concentrated nitric acid (5 ml.) (8 hr.) gave after evaporation to dryness monosodium trifluoromethylphosphonate (0·095 g., 99%); the salt was identified by comparison of its infra-red spectrum with that of an authentic specimen.

(b) *From dichlorotrifluoromethylphosphine.* This compound (0·233 g.) and water (1 ml.) *in vacuo* formed two layers at lower temperatures, but at 20° a vigorous exothermic reaction occurred and a homogeneous solution was obtained. This was completely volatile when evaporated by freeze-drying. Treatment of the condensate with an excess of sodium hydroxide yielded fluoroform (0·092 g., 90%), thus revealing the presence of the volatile trifluoromethylphosphonous acid.

(c) *From iodobistrifluoromethylphosphine.* The iodo-compound (0·484 g.) and water (2 ml.)

reacted at room temperature to form a homogeneous solution (10 min.) and fluoroform (0·114 g., 48%). The solution was completely volatile when freeze-dried, and liberated fluoroform when treated with an excess of sodium hydroxide.

A solution of trifluoromethylphosphonous acid containing hydrogen iodide prepared as above liberated fluoroform quantitatively when heated at 100° for 16 hr. Fluoroform was also liberated quantitatively if the hydrogen iodide was first exactly neutralised by sodium hydroxide and the solution was then heated.

(d) *From di-iodotrifluoromethylphosphine.* Hydrolysis of this phosphine with the *minimum* amount of water yields a white substance when the solution is evaporated to dryness *in vacuo* (see Part VII). This substance, which is formed by decomposition of trifluoromethylphosphonous acid under these conditions, is being studied further. When an excess of water is used for the hydrolysis, evaporation by freeze-drying leaves no residue.

Di-iodotrifluoromethylphosphine (0·72 g.) and water (2 ml.) were allowed to react at 20°, then 3 equiv. of sodium hydroxide (12·45 ml. of 0·496N) and water (5 ml.) were added slowly; no gas was evolved. An aliquot portion, evaporated by freeze-drying, gave a white solid consisting of sodium iodide and sodium trifluoromethylphosphonite. The infra-red spectrum of the mixture was identical with that recorded as above for sodium trifluoromethylphosphonite (sodium iodide is transparent in this region of the infra-red). Addition of an excess of aqueous sodium hydroxide to a solution of the solid caused quantitative evolution of fluoroform.

Infra-red Spectra.—A Perkin–Elmer Model 21 double-beam instrument with rock-salt optics was used. The weak bands near 3 and 6 μ are caused by traces of moisture.

One of the authors (F. W. B.) gratefully acknowledges a scholarship from Wolverhampton Education Committee (1949—1950) and receipt of a D.S.I.R. Maintenance Allowance (1950—1952). The authors thank the D.S.I.R. and the Shell Petroleum Co. for grants to provide special apparatus used in this research.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, March 19th*, 1954.]

Esters of Inorganic Oxyacids. Part I. The Mechanism of Hydrolysis of Alkyl Esters, ^{18}O being used as Tracer, and its Relation to other Reactions in Alkaline Media.

By M. ANBAR, I. DOSTROVSKY, DAVID SAMUEL, and A. D. YOFFE.

[Reprint Order No. 5328.]

The mode of bond fission in the alkaline hydrolysis of a number of esters of inorganic oxyacids has been determined by using ^{18}O-labelled compounds. These include esters of hypochlorous, hypobromous, chloric, bromic, iodic, perchloric, sulphuric, nitrous, nitric, and chromic acid, and also acetic acid. Of the esters studied, only triphenylmethyl perchlorate, sulphate, and nitrate and *tert.*-butyl nitrate are hydrolysed with alkyl–oxygen fission. *n*-Butyl and *n*-octyl nitrates, triphenylmethyl chromate and acetate, and diethyl sulphate are hydrolysed only partly by alkyl–oxygen fission, and the remainder retain the alkyl–oxygen bond in hydrolysis.

The mode of bond fission occurring in the alkaline hydrolysis is discussed in relation to the strength of the acid and the nature of the alkyl group. The relationship of other reactions of these esters, such as alkylation, halogenation, nitration, nitrosation, and oxidation, is discussed.

ESTERS of inorganic oxyacids offer an interesting series for the study of the properties of the C–O–X bonds, where X is the central atom of an oxyacid, and for correlation of the reactions of such esters with the electronegative character of the inorganic acid residue. Many of these esters are used as reagents in organic chemistry (*viz.*, hypochlorites, chromates, nitrites, nitrates, and sulphates). A comparison of such reactions with hydrolysis, on the one hand, and with the properties of the acid and alkyl components of the ester, on the other, may help in unifying and interpreting the various known reactions and in predicting possible new reactions and reagents.

Kinetic measurements for some of these esters have already been reported. *tert.*-Butyl, propyl, and diphenylmethyl nitrites have been studied by Allen (*Nature*, 1953, **172**, 301) who demonstrated that their alkaline hydrolysis proceeds by a nucleophilic attack on nitrogen. Hammett and Lucas (*J. Amer. Chem. Soc.*, 1942, **64**, 1928) have reported the rates of alkaline hydrolysis of *tert.*-butyl and benzyl nitrates. Baker and Easty (*J.*, 1952, 1193, 1208) made an extensive study of the alkaline hydrolysis of methyl, ethyl, *iso*propyl, and *tert.*-butyl nitrates, and showed that the hydrolysis of the *tert.*-butyl ester proceeds by an S_N1 mechanism whereas methyl and ethyl nitrates are hydrolysed by an S_N2 mechanism. They also found that parallel reactions lead to the formation of olefins and oxidation products. In connection with their studies of the mechanism of chromate oxidation, Leo and Westheimer (*J. Amer. Chem. Soc.*, 1952, **74**, 4383) have shown that the rates of hydrolysis of *iso*propyl and *tert.*-butyl chromates are base-catalysed. The kinetics of the formation and hydrolysis of *tert.*-butyl hypochlorite have been investigated in both alkaline and acid media by Anbar and Dostrovsky (*J.*, 1954, 1094). In the alkaline hydrolysis the reaction proceeds by nucleophilic attack on chlorine. The hydrolysis of triphenylmethyl perchlorate has been reported as being both acid- and base-catalysed (Bodforss and Ahrland, *Acta Chem. Scand.*, 1951, **5**, 227).

It appears from the kinetic work summarised above and from general considerations that nucleophilic attack on compounds of the general type C–O–X may occur in several ways: (*a*) A nucleophilic attack of the reagent Y on the α-carbon atom of the alkyl group, denoted by the symbol S_{NC}.* (*b*) A nucleophilic attack of Y on the central atom X of the oxyacid, denoted by S_{NX}. (*c*) An oxidation reaction, similar to the well-known nucleophilic elimination reactions, denoted by O_N. In this case the hydrogen atom attached to the α-carbon atom of the alkyl group is removed by the reagent Y and the group X is detached as an anion, with the formation of a double bond between carbon and oxygen. Each of these schemes may of course proceed by either a bimolecular or a unimolecular mechanism, though not all of the various possibilities have been observed. These schemes are summarised below:

Scheme 1. $Y^- + C\text{–}O\text{–}X \longrightarrow Y\text{–}C + O\text{–}X^-$ . . . . . S_{NC}

Scheme 2. $Y^- + X\text{–}O\text{–}C \longrightarrow Y\text{–}X + CO^-$ . . . . . S_{NX}

Scheme 3. $Y^- + H\text{–}C\text{–}O\text{–}X \longrightarrow YH + C\text{–}O + X^-$ . . . . . O_N

Point of Bond Fission.—In order to distinguish between schemes 1 and 2, the alkaline hydrolysis of a number of esters of inorganic acids was studied, by using water enriched with respect to ^{18}O. In some cases the results were checked by repeating the experiments, esters labelled with ^{18}O in the alkoxy-group and normal water being used.

Many of these esters were synthesised by standard methods (see Experimental section). The hypochlorite, chlorate, bromate, and iodate of triphenylmethanol have not been prepared before (cf. unsuccessful attempts to prepare chlorites, Levi, *Gazzetta*, 1923, **53**, 40). Attempts to prepare esters of permanganic and cyanic acids were unfortunately unsuccessful.

This paper deals in general with tertiary esters of monobasic oxyacids, although a certain number of other esters have been included. These experiments are now being extended to esters of polybasic acids.

The alcohols resulting from each experiment were isolated, purified, and subjected to isotopic analysis. The type of bond fission occurring is indicated in Table 1.

Kinetic studies have shown that a change in the nature of the alkyl group may cause a change in the order of the reaction from bimolecular to unimolecular $S_N2 \longrightarrow S_N1$ (Ingold, "Structure and Mechanism in Organic Chemistry," 1953, Cornell Univ. Press, p. 316). Similarly, in the alkaline hydrolysis of esters of oxyacids we have found that such a change may also alter the point of attack, *i.e.*, from S_{NC} to S_{NX} (cf. Table 1). However, the change in order of the reaction is more sensitive to the nature of the alkyl group. For instance, in the series: phenyl, *n*-alkyl, *sec.*-alkyl, *tert.*-alkyl, triphenylmethyl, hydrogen, there will

* The authors feel that, in spite of the disadvantages of introducing yet another set of symbols, this nomenclature is required since it is more general than that used by Ingold and his co-workers (*Trans. Faraday Soc.*, 1941, **37**, 686) or Dewar ("Electronic Theory of Organic Chemistry," Oxford Univ. Press, p. 111) for the hydrolysis of carboxylic acid esters.

be a tendency for a change in mechanism in the sense $S_{NX}1 \longrightarrow S_{NX}2 \longrightarrow S_{NC}2 \longrightarrow S_{NC}1$ as we proceed from left to right. With any one given acid the range of groups in the above series is insufficient to show the whole sequence of changes, and the series has not been extended sufficiently to the left to show the mechanism $S_{NX}1$. For many acids, portions of the sequence have been observed, as will be discussed later.

TABLE 1.

Ester	Fission by scheme :	Ester	Fission by scheme :
tert.-Butyl hypochlorite	2	*n*-Butyl nitrate	mixed
tert.-Butyl hypobromite	2	*n*-Octyl nitrate	mixed
Triphenylmethyl hypochlorite	2	*tert.*-Butyl nitrate	1
,, chlorate	2	Triphenylmethyl nitrate	1
,, bromate	2	Bistriphenylmethyl sulphate	1
,, iodate	2	Diethyl sulphate	mixed
,, perchlorate	1	Di-*tert.*-butyl chromate	2
n-Butyl nitrite	2	Bistriphenylmethyl chromate	mixed
tert.-Butyl nitrite	2	*tert.*-Butyl acetate	2
Triphenylmethyl nitrite	2	Triphenylmethyl acetate	mixed

It is clear from the above considerations that if the triphenylmethyl ester of a given acid is hydrolysed by an S_{NX} mechanism (scheme 2) the hydrolysis of all esters of the same acid to the left of triphenylmethyl in the series above will also follow the same mechanism. Table 1 shows that the triphenylmethyl esters of hypohalogenous, halogenic, and nitrous acids are hydrolysed by mechanism S_{NX}, probably by a bimolecular nucleophilic attack on atom X. It may therefore be safely concluded that all other esters of these acids will also hydrolyse by the same mechanism, typified by $RO\overset{+}{-}ClO^{-}$.

Influence of Acid Strength.—Examination of Table 1 shows that, in general, esters hydrolysing by mechanism 2 are those of weak inorganic acids. With esters of strong acids, a rough correlation may be expected between the strength of the acid, which is a measure of its tendency to given up a proton, and the ease of alkyl–oxygen fission. In fact, the esters of the strongest acids and very electropositive alkyl groups are known to be partially ionic (Hantzsch, *Ber.*, 1930, **63**, 1181; 1921, **54**, 2573).

For this reason triphenylmethyl perchlorate, sulphate, and nitrate are hydrolysed with alkyl–oxygen fission, presumably by an $S_{NC}1$ mechanism.

However, Bodforss and Ahrland (*loc. cit.*) report that the hydrolysis of triphenylmethyl perchlorate is subject to both acid and alkaline catalysis. This is inconsistent with our isotopic results unless one assumes a nucleophilic attack on the α-carbon atom of the triphenylmethyl group, which is most unlikely. Our attempts to repeat their work and measure the rate of hydrolysis of this perchlorate were unsuccessful owing to the almost instantaneous reaction.

In a series of esters of an inorganic acid where the alkyl group is progressively replaced by less electropositive groups, a change in mechanism from 1 to 2 will occur at some point. This point will be reached earlier for the weaker acids and it may require a very electronegative group to cause a change in mechanism in the hydrolysis of esters of the stronger acids.* Thus in the case of the chromates and acetates a change in mechanism already occurs in passing from triphenylmethyl to *tert.*-butyl. This conclusion is borne out by the work of Kenyon and his co-workers, who used optically active carboxylic esters of certain secondary alcohols (Kenyon and Mason, *J.*, 1952, 4964 and previous papers). They observed that small changes in conditions are sufficient to change the mode of bond fission.

In the hydrolysis of esters of a stronger acid, such as nitric acid, the isotopic results show that the change in mechanism occurs with the normal alkyl ester.

Baker and Easty (*loc. cit.*) have observed bimolecular alkaline hydrolysis of normal alkyl nitrates and have assumed a nucleophilic attack on carbon. Their results should be reinterpreted in terms of the present work as involving nucleophilic attack also on nitrogen. This interpretation is supported by the work of Ansell and Honeyman (*J.*, 1952,

* In acid media a similar situation prevails except that the change in mechanism occurs earlier. Hydrolysis in acid media will form the subject of a separate paper.

2778) on the hydrolysis of sugar nitrates and of Horne and Shriner (*J. Amer. Chem. Soc.*, 1933, **55**, 4652) on the nitration of cyclic ketones with optically active nitrates.

Bunton and Frei's results (*J.*, 1951, 1872) show that the alkaline hydrolysis of phenyl toluene-*p*-sulphonate occurs by scheme 2. On the other hand, we have found that *n*-alkyl sulphates are hydrolysed mainly with alkyl–oxygen fission. In view of the close similarity in the strength of toluene-*p*-sulphonic acid and sulphuric acid it may be concluded that in the sulphates a change in mechanism probably occurs between the phenyl and the *n*-alkyl groups.

On comparing the triphenylmethyl esters of oxyacids of a given element varying in the degree of oxidation of the oxyacids, a tendency for the ester of the highest oxidation state, *i.e.*, corresponding to the strongest acid, to hydrolyse by mechanism 1 is evident, whereas those of the lower oxidation state react by scheme 2. For instance, in the series RO–Cl, RO–ClO (postulated), RO–ClO_2, R–$OClO_3$, the change in mechanism occurs between chlorate and perchlorate. No chlorite esters are known but it can be safely assumed that all chlorites would be hydrolysed according to scheme 2.

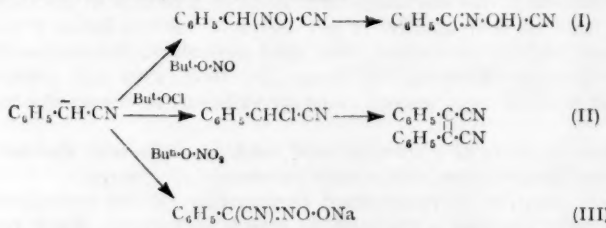
Similarly, in the oxyacids of nitrogen all nitrites react by mechanism 2 whereas tertiary nitrates react by mechanism 1, *i.e.*, RO–NO, R–ONO_2.

Cationic Reactions.—Other reactions of the esters of inorganic oxyacids may be related to the mechanism of alkaline hydrolysis, since, in the reaction schemes outlined above, the reagent Y may be any nucleophilic molecule and need not be limited to the hydroxyl ion. Thus reactions by scheme 1 (S_{NC}) will lead to ether formation if $Y = RO^-$ or to alkylation if $Y = \geqslant C^-$, or $>N^-$, while those proceeding by scheme 2 (S_{NX}) will lead to trans-esterification if $Y = RO^-$ and to halogenation, nitration, nitrosation, etc., if $Y = \geqslant C^-$ or $>N^-$. Numerous examples are available to illustrate these points. The use of dimethyl and diethyl sulphates as alkylating agents in alkaline media is well known, alkylation by *tert.*-butyl perchlorate has been reported (Cauquil, Barrera, and Barrera, *Bull. Soc. chim.*, 1953, **20**, 1111), and *N*-alkylation by triphenylmethyl nitrate and diphenylmethyl nitrate has recently been described by Cheeseman (*Chem. and Ind.*, 1954, 281).

The above esters have been shown to undergo hydrolysis by mechanism S_{NC}. Although it is the tertiary alkyl group which promotes reaction by this mechanism, the considerable steric hindrance associated with this group often limits the use of these esters as alkylating agents.

Halogenation by hypohalites has been discussed by Anbar and Ginsburg (*Chem. Reviews*, in the press). Nitration by *n*-alkyl nitrates and nitrosation by alkyl nitrites are well-known procedures (cf. Sidgwick, "Organic Chemistry of Nitrogen," Oxford Univ. Press, 1937, pp. 4, 8). These esters undergo hydrolysis by mechanism S_{NX}. As a further illustration, the action of *tert.*-butyl hypochlorite, nitrate, and nitrite and of *n*-butyl nitrate on benzyl cyanide in alkaline media has been examined.

From the reaction of the hypochlorite, diphenyl maleinitrile (II) was isolated. In the nitrite reaction the oxime (I) of phenylglyoxylonitrile was formed, and *n*-butyl nitrate gave a 70% yield of the sodium salt of *aci*nitrophenylacetonitrile (III). These results are consistent with the following reaction schemes:



tert.-Butyl nitrate, on the other hand, with benzyl cyanide in alcoholic sodium ethoxide gives a quantitative yield of sodium nitrate and some *tert.*-butyl ethyl ether. No nitration products could be isolated, indicating the absence both of any trans-esterification with the solvent and of direct nitration.

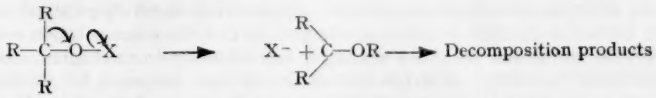
Trans-esterification and Oxidation Reactions.—Tertiary alkyl esters can undergo reactions only by schemes 1 and 2. In compounds hydrolysing by scheme 2 (Y = OR^-) (see p. 3604), trans-esterification is always possible : $RO^- + X{-}O{-}C \longrightarrow ROX + {}^-O{-}C$, and therefore in a mixture of a tertiary ester and a secondary or primary alcohol, a certain proportion of the ester of this alcohol will be formed. Once such an ester is formed, it will react further by schemes 2 and 3. Two possibilities exist for reaction by the latter scheme, namely, free-radical or ionic reactions. Under appropriate conditions, in the vapour or liquid phase and in solution in non-ionising solvents, the ester may decompose by a free-radical mechanism to give oxidation products (Waters, see Gilman, " Organic Chemistry," Vol. IV, Chap. 12, 1953; Kharasch, Fono, Nudenberg, and Bischof, *J. Org. Chem.*, 1952, **17**, 209 and previous papers; Steacie, " Atomic and Free Radical Reactions," Reinhold, 1946).

In alkaline aqueous media, for esters which are hydrolysed with alkyl–oxygen fission, olefin elimination by mechanisms *E*1 and *E*2 will compete with the substitution reaction in proportions which depend on the nature of the alkyl group and the conditions of reaction (Ingold, *op. cit.*, Ch. 8). On the other hand, for esters undergoing hydrolysis by mechanism S_{NX}, the reaction analogous to olefin formation is scheme 3 (cf. p. 3604), leading to oxidation products (see also Kornblum and De la Mare, *J. Amer. Chem. Soc.*, 1951, **73**, 880) : $Y^- + H{\cdot}C{\cdot}O{\cdot}X \longrightarrow YH + C{=}O + X^-$. This will occur only when the negatively charged group X^- is stable. Thus, whereas primary and secondary hypochlorites are oxidised, the corresponding nitrites are stable towards this reaction.

It follows that for a tertiary ester to be a useful oxidising agent for alcohols it should (*a*) undergo hydrolysis by scheme 2 and therefore be capable of trans-esterification, and (*b*) give a stable X^- group. Hence, tertiary perchlorates, sulphates, and nitrates, which are hydrolysed by scheme 1, are not oxidising agents since they do not fulfil condition (*a*). It should be noted that primary and secondary nitrates, which tend to hydrolyse by scheme 2, when formed by other methods give a certain proportion of oxidation products (Baker and Easty, *loc. cit.*; Lucas and Hammett, *loc. cit.*).

On the other hand, *tert.*-butyl nitrite and acetate, although undergoing trans-esterification, do not oxidise other alcohols since the groups NO^- and $CH_3{\cdot}CO^-$ are unstable. All other tertiary esters listed in Table 1 are oxidising agents in that they fulfil both the conditions outlined above; cf. *tert.*-butyl hypochlorite (Anbar and Ginsburg, *loc. cit.*; Grob and Schmid, *Helv. Chim. Acta*, 1953, **36**, 1763), chromate (Leo and Westheimer, *loc. cit.*), also the oxidation of *iso*propyl alcohol by bromate to acetone (Farkas and Uri, *Chem. Abs.*, 1951, **45**, 1498).

In addition to these reactions, rearrangements may accompany reactions proceeding by scheme 2. The rearrangement is analogous to that of Wagner and Meerwein, and involves an internal nucleophilic attack on oxygen :



A similar mechanism has been suggested in the decomposition of certain hydroperoxides (Kharasch *et al.*, *loc. cit.*; Bartlett and Cotman, *J. Amer. Chem. Soc.*, 1950, **72**, 3095), and should be particularly prominent in triphenylmethyl esters analogously to the hydrolysis of triphenylethyl chloride (Charlton, Dostrovsky, and Hughes, *Nature*, 1951, **167**, 986). Triphenylmethyl esters which are hydrolysed by mechanism 1 do not of course undergo this rearrangement, and hydrolysis is clean. Similarly, the nitrite ester, provided no thermal decomposition sets in, is hydrolysed cleanly and gives a quantitative yield of the carbinol. On the other hand the hypochlorite, chlorate, bromate, and iodate give varying amounts of breakdown products such as benzophenone, diphenyl, and phenol.

Experimental

Preparation of Esters.—*tert.*-Butyl hypochlorite and hypobromite were prepared by the methods described by Anbar and Dostrovsky (*loc. cit.*).

Triphenylmethyl hypochlorite was prepared by shaking a suspension of triphenylmethanol

(1·3 g.) in a carbon tetrachloride solution of chlorine monoxide (30 ml.; 0·2M) in the presence of anhydrous sodium sulphate (10 g.). After 24 hours' shaking at room temperature, the solution was decanted and concentrated to half its volume in a vacuum. Some unchanged carbinol was filtered off, and the filtrate evaporated to dryness in a vacuum in a vessel protected from light. Golden-yellow crystals were obtained which were hydrolysed rapidly on exposure to moist air and were very soluble in carbon tetrachloride The substance is hydrolysed immediately in aqueous media and the solution is free from chloride ion but contains active chlorine as hypochlorous acid. From the hydrolysis mixture there were isolated in addition to the carbinol small quantities of benzophenone, diphenyl, and phenol.

Triphenylmethyl chlorate was prepared by shaking a solution of triphenylmethyl chloride (5 g.) in carbon tetrachloride (60 ml.) with silver chlorate (9 g.) for 12 hr. at room temperature. The silver chlorate was prepared from sodium chlorate and silver nitrate ("Inorganic Syntheses," Vol. II, p. 4). The yellow-orange solution was decanted and concentrated to dryness in a vacuum. Orange crystals were obtained which were free from chloride ion. The solution becomes brown-black on hydrolysis in alkali. The dark solution contained, in addition to the carbinol, oxidation and decomposition products.

Triphenylmethyl bromate and iodate were prepared by a method similar to that described above, by use of silver bromate and silver iodate, respectively. Both form orange crystals. In the case of triphenylmethyl iodate, ether was used as the solvent since this iodate is insoluble in carbon tetrachloride.

Triphenylmethyl perchlorate, prepared from 70% perchloric acid and triphenylmethanol in acetic anhydride (Hofmann and Kirmreuther, *Ber.*, 1909, **42**, 4861), was isolated as brown crystals.

Diethyl sulphate, *n*-butyl nitrite, and *tert.*-butyl acetate were commercial products and were purified by fractional distillation before use.

tert.-Butyl nitrite was prepared by a modification of the method in "Organic Syntheses" (Coll. Vol. II, p. 108), in which concentrated sulphuric acid was added slowly to a cooled aqueous solution of sodium nitrite and *tert.*-butanol.

Triphenylmethyl nitrite was prepared by the action of liquid dinitrogen trioxide at −10° on an ether solution of triphenylmethanol. The solution was concentrated to one third of its volume under vacuum, and the triphenylmethyl nitrite filtered off, washed with dry light petroleum, and dried in a vacuum (P_2O_5). This is a modification of the method used by Schlenk, Mair, and Bornhardt (*Ber.*, 1911, **44**, 1169). Analyses for the nitrite content of this ester by Griess's method gave values ranging between 80 and 90% for the conversion of carbinol into nitrite ester.

n-Butyl nitrate was prepared by reaction of *n*-butanol with nitric and sulphuric acids (Shriner, *J. Amer. Chem. Soc.*, 1933, **55**, 768). *n*-Octyl nitrate was prepared from octyl bromide and silver nitrate in acetonitrile (Ferris, McLean, Marks, and Emmons, *ibid.*, 1953, **75**, 4078). *tert.*-Butyl nitrate was prepared from *tert.*-butyl chloride and silver nitrate (Baker and Easty, *J.*, 1952, 1202). Triphenylmethyl nitrate was prepared by shaking an ether or carbon tetrachloride solution of triphenylmethyl chloride with silver nitrate until chloride ion was no longer detected. The carbon tetrachloride solution was yellow, and the ether solution colourless.

Di-*tert.*-butyl chromate was prepared in carbon tetrachloride from chromic oxide and *tert.*-butanol (Westheimer, *loc. cit.*). Bistriphenyl chromate was prepared by shaking a carbon tetrachloride solution of triphenylmethyl chloride with silver chromate. The red-orange solution is unstable and slowly decomposes.

Triphenylmethyl acetate, prepared from triphenylmethyl chloride and silver acetate (Gomberg, *Ber.*, 1902, **35**, 1835), had m. p. 86—88°.

Bistriphenylmethyl sulphate was prepared by shaking a carbon tetrachloride solution of triphenylmethyl chloride with silver sulphate.

In attempts to prepare *tert.*-butyl and triphenylmethyl permanganate by refluxing a carbon tetrachloride solution of the corresponding chloride with silver permanganate, no reaction was observed, even after 12 hr.

Attempts to prepare *tert.*-butyl iodate included shaking *tert.*-butyl chloride and silver iodate in carbon tetrachloride or acetonitrile solutions, refluxing *tert.*-butyl alcohol and iodine pentoxide in carbon tetrachloride, and shaking an aqueous solution of *tert.*-butanol and iodic acid in the presence of carbon tetrachloride. In no case did reaction occur.

^{18}O-*Alkoxy-labelled Esters.*—^{18}O-Labelled *tert.*-butyl nitrite, chromate, and hypochlorite were prepared by shaking ^{18}O-labelled *tert.*-butanol (cf. Anbar and Dostrovsky, *loc. cit.*) with an aqueous solution of the acid in the presence of dilute sulphuric acid and carbon tetrachloride.

After 4 hours' shaking at room temperature, the carbon tetrachloride layer was separated and washed with water until free from alcohol. The esters were not isolated and the solutions in carbon tetrachloride were used directly in further experiments. In each case a slow acid-catalysed exchange occurs between water and *tert.*-butanol (see Dostrovsky and Klein, *J.*, to be published). Therefore the unchanged alcohol from the aqueous layer was isolated and analysed for ^{18}O content as a check. In no case did the exchange amount to more than 5%.

^{18}O-Labelled nitrites were also prepared from ^{18}O-labelled *tert.*-butanol and liquid dinitrogen tetroxide at 0° (cf. Yoffe and Gray, *J.*, 1951, 1412), and from *tert.*-butanol and liquid nitrosyl chloride in pyridine at 0°. ^{18}O-Labelled *tert.*-butyl acetate was prepared from ^{18}O-labelled *tert.*-butanol, acetyl chloride, and pyridine in xylene solution by the method used by Bogart and Smith (*J. Amer. Chem. Soc.*, 1936, **58**, 1016) for the unlabelled ester.

Hydrolyses of Esters in ^{18}O-Labelled Water.—A 5N-sodium hydroxide stock solution was prepared from the required amount of a 3% sodium amalgam and water enriched in ^{18}O. This was diluted with enriched water as required.

The results of the isotopic experiments are summarised in Tables 2 and 3.

TABLE 2. *Hydrolysis of unlabelled esters in aqueous alkali labelled with ^{18}O.*

Ester	Atom % excess of ^{18}O in: hydrolysis medium	alcohol from hydrolysis	% Alkyl–oxygen fission	Ester	Atom % excess of ^{18}O in: hydrolysis medium	alcohol from hydrolysis	% Alkyl–oxygen fission
$Bu^t{\cdot}OCl$	0·87	0·00	0	$C_8H_{17}{}^n{\cdot}O{\cdot}NO_2$	2·00	0·51	15
$Bu^t{\cdot}OBr$	1·35	0·00	0	$Bu^t{\cdot}O{\cdot}NO_2$	1·35	1·35	100
$Ph_3C{\cdot}OCl$	1·35	0·00	0	$Ph_3C{\cdot}O{\cdot}NO_2$	1·67 *	1·51	91
$Ph_3C{\cdot}O{\cdot}ClO_3$	1·35	0·01	1	$(Bu^tO)_2CrO_2$	1·35	0·05	4
$Ph_3C{\cdot}O{\cdot}BrO_2$	1·35	0·00	0	$(Ph_3C{\cdot}O)_2CrO_2$	1·67 *	1·10	66
$Ph_3C{\cdot}O{\cdot}IO_2$ ...	1·35	0·01	1	$Bu^t{\cdot}OAc$	2·00	0·08	4
$Ph_3C{\cdot}O{\cdot}ClO_3$	1·84	1·75	95	$Ph_3C{\cdot}OAc$ ...	1·32 *	0·88	67
$Bu^n{\cdot}O{\cdot}NO$ ...	2·00	0·00	0	$(Ph_3C{\cdot}O)_2SO_2$	1·67 *	1·56	93
$Bu^t{\cdot}O{\cdot}NO$ ...	1·35	0·00	0	$(EtO)_2SO_2$ ...	1·72	1·47	85
$Ph_3C{\cdot}O{\cdot}NO$ ...	1·35	0·01	1	$Ph_3C{\cdot}OH$ † ...	1·35	0·00	0
$Bu^n{\cdot}O{\cdot}NO_2$ ...	1·35	0·44	33				

* Atom % excess ^{18}O in triphenylmethanol obtained by hydrolysis of stock triphenylmethyl chloride solution in the ^{18}O labelled medium.

† Control experiment showing absence of oxygen-exchange between triphenylmethanol and aqueous alkali.

TABLE 3. *Hydrolysis of ^{18}O-alkoxy-labelled esters in N-aqueous alkali.*

Ester	Atom % excess of ^{18}O in: alkoxy-group	alcohol from hydrolysis	% Alkyl–oxygen fission	Ester	Atom % excess of ^{18}O in: alkoxy-group	alcohol from hydrolysis	% Alkyl–oxygen fission
$Bu^t{\cdot}OCl$	0·86	0·85	1	$Bu^t{\cdot}OAc$	1·60	1·54	4
$Bu^t{\cdot}O{\cdot}NO$ ...	1·60	1·59	0	$(Bu^tO)_2CrO_2$	1·60	1·42	10

(i) *n*-Butyl nitrite (2 g.) of normal isotopic composition was shaken for 14 days at room temperature with 2·5N-aqueous sodium hydroxide solution (20 ml.) enriched with respect to ^{18}O, and the aqueous layer separated and fractionated. The azeotrope of alcohol and water was dried (K_2CO_3). A second drying was carried out with vigorous shaking at 60° for 3 hr. The alcohol was then analysed for its ^{18}O content by Anbar, Dostrovsky, Klein, and Samuel's procedure (*J.*, in the press).

(ii) *n*-Butyl nitrate (3 g.) was dissolved in a mixture of N-aqueous sodium hydroxide (30 ml.) enriched in ^{18}O and absolute ethanol (40 ml.). The solution was refluxed for 8 days in a stainless-steel vessel and then extracted with carbon tetrachloride to remove unchanged nitrate ester. The aqueous layer was fractionated carefully, and the butanol dried and analysed as above. A similar procedure was used for *n*-octyl nitrate.

(iii) *tert.*-Butyl nitrate (1·2 g.) was shaken for 24 hr. with N-aqueous sodium hydroxide (10 ml.) enriched in ^{18}O. The alcohol was distilled out, dried, and analysed as above.

(iv) Diethyl sulphate * and *tert.*-butyl acetate were refluxed with N-aqueous sodium hydroxide enriched in ^{18}O. The aqueous layer was fractionated, and the alcohol dried and analysed.

(v) *tert.*-Butyl hypobromite was hydrolysed with aqueous sodium hydroxide enriched in ^{18}O according to the procedure for the hypochlorite (cf. Anbar and Dostrovsky, *loc. cit.*).

* We thank Dr. Halmann for making the results of this experiment available to us.

(vi) *tert.*-Butyl chromate in carbon tetrachloride solution (10 ml., 0·5 ml.) was refluxed with 5N-aqueous sodium hydroxide (20 ml.) enriched in ^{18}O. The aqueous layer was extracted with carbon tetrachloride and fractionated. The alcohol was dried and anlysed as above. In the aqueous layer a quantitative amount of chromate was found by analysis as barium chromate.

(vii) *Hydrolysis of triphenylmethyl esters.* In the hydrolysis of triphenylmethyl esters the following procedure was used for the sulphate, nitrate, chromate, chlorate, bromate, and iodate. A stock solution of triphenylmethyl chloride (0·3M) in carbon tetrachloride was prepared. Aliquot portions (30 ml.) were shaken with the corresponding silver salt until reaction was complete, as judged by the absence of chloride ion upon the hydrolysis of a test sample. The carbon tetrachloride solution of the ester was decanted into an excess of 4N-aqueous solution of sodium hydroxide enriched in ^{18}O and shaken at room temperature until hydrolysis was completed. The carbinol formed, being only slightly soluble in the carbon tetrachloride, collected at the interface and was filtered off, washed with water and carbon tetrachloride, recrystallised from benzene, and analysed for ^{18}O by the method described below.

The aqueous phase resulting from the hydrolysis of the chromate ester was analysed for chromate gravimetrically as barium chromate. The amount obtained was in satisfactory agreement with the mass of carbinol isolated.

Triphenylmethyl acetate is hydrolysed very slowly unless the experiment is carried out as a homogeneous reaction. The ester was therefore prepared in dioxan as solvent from silver acetate and triphenylmethyl chloride and was refluxed for several days at 100°. In order to avoid errors due to the presence of small amounts of carbinol in the triphenylmethyl chloride solutions and to systematic errors in the analysis, portions of the triphenylmethyl chloride stock solution were hydrolysed with the same enriched sodium hydroxide solution and the ^{18}O content of the resulting carbinol was used in computing the percentage of alkyl–oxygen fission of the esters. Nevertheless, a small amount of decomposition occurs which leads to the formation of small quantities of carbinol and to slightly low results in the isotopic analysis. No oxygen exchange was detected in several experiments in which triphenylmethanol (2 g.) was refluxed with a mixture of ethanol (20 ml.) and aqueous sodium hydroxide enriched in ^{18}O (5 ml.; 1N). In the case of triphenylmethyl perchlorate, nitrite, and hypochlorite, the crystalline ester (3 g.) was shaken in excess of N-sodium hydroxide enriched in ^{18}O at room temperature until hydrolysis was complete, and the carbinol isolated and analysed.

The aqueous solution resulting from the hydrolysis of the nitrite ester was analysed for nitrite by Griess's method.

Analysis of Triphenylmethanol for ^{18}O content.—The ^{18}O content of the triphenylmethanol obtained from the hydrolysis experiments was determined as follows: Dry hydrogen chloride was bubbled through a benzene solution of the carbinol (1·5 g. in 12 ml. of dry benzene) for several minutes until all the carbinol was converted into triphenylmethyl chloride. The turbid solution was then centrifuged until the water (*ca.* 0·1 ml.) separated at the bottom. By means of a micro-pipette, 30 mg. of the water were introduced into a sealed tube, and the ^{18}O content of the water determined by equilibration overnight with carbon dioxide at 70°, and analysis of the carbon dioxide in a mass-spectrometer.

Hydrolysis of ^{18}O-Labelled Esters.—(*a*) The carbon tetrachloride solution of ^{18}O-labelled *tert.*-butyl nitrite and hypochlorite was shaken at room temperature with a large excess of N-sodium hydroxide for 14 days. The aqueous layer was then separated, extracted with carbon tetrachloride to remove unchanged ester, and fractionated. The azeotrope was treated with potassium carbonate, and the alcohol dried and analysed as before.

(*b*) A carbon tetrachloride solution (10 ml.; 0·5M) of ^{18}O-labelled di-*tert.*-butyl chromate was refluxed with excess of 5N-sodium hydroxide (20 ml.) for 12 hr. The carbon tetrachloride layer was washed several times with dilute sodium hydroxide and the combined aqueous phase was distilled. The azeotrope was treated as above.

(*c*) ^{18}O-Labelled *tert.*-butyl acetate was refluxed with 4N-sodium hydroxide for 5 days. After separation of the unchanged ester the aqueous layer was extracted with carbon tetrachloride, and fractionated. The azeotrope was treated as above and analysed.

Cationic Reactions.—Nitrosation. A mixture of benzyl cyanide (1·5 g.) and *tert.*-butyl nitrite (1·4 g.) was added slowly to a stirred solution of metallic potassium (0·8 g.) in *tert.*-butanol (20 c.c.). After a further 10 minutes' stirring, the solution was poured into a large volume of cold water, acidified, and extracted with ether. On evaporation of the ether, a solid remained which, crystallised from hot water (twice; 1 g.; m. p. 128°), was identified as the oxime of phenylglyoxylonitrile (cf. Wislicenus, *Ber.*, 1888, **21**, 1314).

Nitration. A mixture of benzyl cyanide (1·2 g.) and *n*-butyl nitrate (1·2 g.) was added with

stirring to an ice-cold solution of sodium (0·25 g.) in dry ethanol (10 g.). A white precipitate (0·8 g.) was formed which was identified as the sodium salt of *aci*-nitrophenylacetonitrile (cf. *idem*, *Ber.*, 1902, **35**, 1755).

When a mixture of *tert.*-butyl nitrate (2·3 g.) and benzyl cyanide (2·3 g.) was added slowly to an ice-cold solution of sodium (0·5 g.) in dry ethanol (20 c.c.), an immediate precipitate (1·5 g.) was formed which was identified as sodium nitrate. The filtrate was poured into water (100 ml.) saturated with sodium sulphate and extracted with ether. The ether layer was dried and fractionally distilled. A small quantity of *tert.*-butyl ethyl ether, b. p. 66—67°, was obtained.

From a parallel experiment unchanged benzyl cyanide (1 g.) was recovered from the ethanolic solution upon fractionation. No ethyl nitrate could be detected in the products of the alcoholysis of *tert.*-butyl nitrate.

Chlorination. An ice-cold mixture of benzyl cyanide (2 g.) and *tert.*-butyl hypochlorite (2·5 g.) was slowly added with stirring to an ice-cold solution of potassium (0·8 g.) in *tert.*-butanol (10 ml.). The solution became dark brown and stirring was continued for 1 hr. The precipitate was filtered off and distilled *in vacuo*. At 200—210°/5 mm. a light yellow liquid distilled over, which solidified. The solid was recrystallised from benzene and identified as diphenylmaleinitrile (0·5 g.; m. p. 150°) (cf. Michael and Jeanpretre, *Ber.*, 1892, **25**, 1681).

The authors thank Dr. F. S. Klein for the mass-spectrometric analyses.

Department of Isotope Research,
Weizmann Institute of Science, Rehovot, Israel. [*Received, April 23rd*, 1954.]

---

*Chebulinic Acid. Part II.**

By R. D. Haworth and L. B. de Silva.

[Reprint Order No. 5461.]

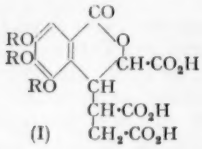
In agreement with Schmidt's formula (I; R = H) for chebulic acid, it has been shown (*a*) that a synthetic mixture of racemates of the γ-lactone (III; R = OH) of 1-hydroxybutane-1 : 2 : 3 : 4-tetracarboxylic acid gave 2·6 mols. of oxalic acid on oxidation with permanganate and (*b*) that 5 : 6 : 7-trimethoxy*iso*coumarin-3-carboxylic acid (IX; R = H) and succinic acid are products of pyrolysis of trimethylchebulic acid in presence of copper powder. Other pyrolytic products include optically active and inactive methyl esters, $C_{17}H_{18}O_8$, and the constitution of the former is discussed in light of the available chemical and spectroscopic evidence.

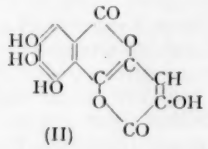
Our interest in chebulinic acid, the crystalline constituent of myrobalans, was aroused by a suggestion by Schmidt and Mayer (*Annalen*, 1951, **571**, 1) that " split acid " (now known as chebulic acid) (Schmidt, Lademann, and Himmele, *Chem. Ber.*, 1952, **85**, 408), a hydrolysis product of chebulinic acid, was an *iso*coumarin derivative of structure (I; R = H), which may be derived from ellagic acid by oxidative degradation of one of the phenolic rings. In view of the possibility of a relation between chebulic acid (I; R = H) and galloflavin, for which the *iso*coumarin structure (II) was tentatively suggested by Haworth and McLachlan (*J.*, 1952, 1583), we investigated chebulic acid; our oxidation (Part I *) of trimethylchebulic acid (I; R = Me) with potassium ferricyanide to 3 : 4 : 5-trimethoxyphthalic acid confirmed the structure of the aromatic moiety. Further evidence in this direction was obtained in the present work when it was found that oxalic, succinic, and trimethylgallic acid were produced by fusing trimethylchebulic acid with potassium hydroxide.

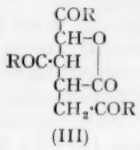
Schmidt and Mayer (*loc. cit.*) oxidised trimethylchebulic acid with permanganate to a lactonic tribasic acid (III; R = OH), the structure of which was supported by reasons summarised in Part I. More recently Schmidt, Mayer, and Wick (*Chem. Ber.*, 1953, **86**, 488) synthesised the two racemates of the isomeric γ-lactone (IV) of 2-hydroxybutane-1 : 2 : 3 : 4-tetracarboxylic acid, and showed that whilst the lactonic acid (III; R = OH)

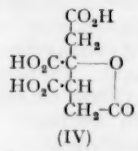
* *J.*, 1951, 3511, is now regarded as Part I.

gave 2·58 mols. of oxalic acid when oxidised with permanganate, the synthetic lactone (IV) yielded only 0·32 mol. More direct confirmatory evidence for structure (III; R = OH) has now been obtained by the synthesis of an oily mixture of racemates having this structure (III; R = OH). Tetraethyl propane-1 : 1 : 2 : 3-tetracarboxylate was isolated during these experiments, and a compound, possibly α-dicarbamoylmethylsuccinimide (V), was prepared by the action of ammonia on tetraethyl propane-1 : 1 : 2 : 3-tetracarboxylate. Wislicenus and Schwanhausser (*Annalen*, 1897, **297**, 107) prepared triethyl 4 : 5-dioxo*cyclo*pentane-1 : 2 : 3-tricarboxylate (VI) by the action of diethyl oxalate on triethyl carballylate in presence of sodium ethoxide, and Gault (*Compt. rend.*, 1910, **150**, 1341) reported the formation of a mixture of (VI) and triethyl ethoxalyltri-


(I)

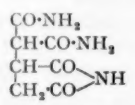

(II)

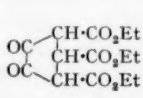

(III)

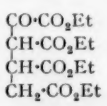

(IV)

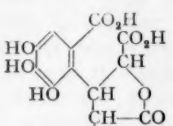
carballylate (VII) without specifying reaction conditions. In the Experimental section we describe conditions which reduce the proportion of the *cyclo*pentanedione derivative (VI) to a minimum and, although the tetraethyl ester (VII) could not be purified because decarbonylation to tetraethyl propane-1 : 1 : 2 : 3-tetracarboxylate took place on heating, it was readily reduced by hydrogen in the presence of Raney nickel to the γ-lactone (III; R = OEt) of triethyl 1-hydroxybutane-1 : 2 : 3 : 4-tetracarboxylate. Although a crystalline triamide (III; R = NH_2) was prepared, this triethyl ester (III; R = OEt) and the hygroscopic acid obtained from it by hydrolysis are probably racemic mixtures. The hygroscopic acid (III; R = OH) was readily oxidised with alkaline permanganate, and the production of 2·6 mols. of oxalic acid confirm the structural views of Schmidt and Mayer (*loc. cit.*) concerning the hydroxybutanetetracarboxylic acid derived from chebulic acid.

These results may be interpreted on the basis of the *iso*coumarin structure (I; R = H) for chebulic acid, as suggested by Schmidt and Mayer (*loc. cit.*), but structure (VIII) is equally consistent with them. The latter γ-lactone structure however is probably excluded by our measurements of the infra-red absorption spectra of chebulic acid derivatives. Trimethyl trimethylchebulate (Schmidt, Heintzeler, and Mayer, *Chem. Ber.*, 1947, **80**, 514) shows a single broad band with a peak at 1740 $cm.^{-1}$, and points of 50% absorption between 1700 and 1790 $cm.^{-1}$; and trimethylchebulic triamide, m. p. 254° (decomp.) (Schmidt and Mayer, *loc. cit.*), has a sharp band at 1727 $cm.^{-1}$, and a broad intense band at 1666—1695 $cm.^{-1}$. The latter is probably due to the amide-carbonyl group (Grove and Willis, *J.*, 1950, 877), and the high-frequency bands are ascribable to six-membered ring lactonic structures such as (I).


(V)


(VI)

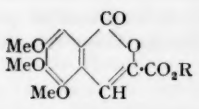

(VII)

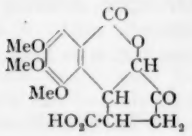

(VIII)

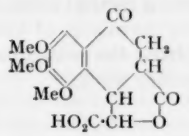
Numerous attempts to dehydrogenate trimethylchebulic acid (I; R = Me) with palladium, sulphur, or selenium were abortive, and the lactone ring was not affected by sodium bismuthate or potassium cyanide. Decarboxylation with copper or copper chromite in boiling quinoline gave oils, but very interesting results have been obtained by pyrolysis of trimethylchebulic acid with copper powder at 260—290°/0·5 mm. An oily sublimate was obtained, and, after methylation with diazomethane, the ester mixture was separated by distillation followed by chromatography on a charcoal column into (*a*) methyl 5 : 6 : 7-trimethoxy*iso*coumarin-3-carboxylate (IX; R = Me), m. p. 154—155°, (*b*) an optically active methyl ester (A), m. p. 149°, of a keto-lactonic acid, $C_{16}H_{16}O_8$, possibly (XI), and (*c*) an optically inactive ketonic methyl ester (B), $C_{17}H_{18}O_8$, m. p. 141°. The

methyl 5 : 6 : 7-trimethoxy*iso*coumarin-3-carboxylate (IX; R = Me) was converted into the corresponding acid (IX; R = H), from which the acid chloride and ethyl ester were prepared, and these product were identified by comparison with the corresponding synthetic substances described in the following paper. The production of the ester (IX; R = Me) during the pyrolysis is readily interpreted on the basis of Schmidt's formula (I; R = H) for chebulic acid as a type of reversed Michael reaction. In agreement with this, the most volatile fraction Y (p. 3615) of the pyrolysis products yielded, on hydrolysis, a small amount of solid which gave a green fluorescence with resorcinol and concentrated sulphuric acid, indicative of succinic acid.

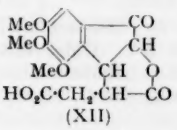
The keto-ester B gave crystalline phenyl- and 2 : 4-dinitrophenyl-hydrazones, but further experiments on it await accumulation of more material. Considerable progress has however been made in elucidating the constitution of the ester (A), although a final solution has not been reached. The derived acid, $C_{16}H_{16}O_8$, gave a crystalline *p*-nitrobenzyl ester, and titration showed the presence of a lactone group in addition to the carboxyl group. Oxidation of the acid with potassium ferricyanide gave 3 : 4 : 5-trimethoxyphthalic acid, but as the methyl ester A did not react with ferric chloride or 3 : 5-dinitrobenzoyl chloride and gave a negative Zerewitinoff test hydroxyl groups were absent. The methyl ester however gave a crystalline phenylhydrazone and a red amorphous 2 : 4-dinitrophenylhydrazone, proving the presence of a ketonic group and accounting for the eighth oxygen atom. The high optical rotation and sparing solubility in water of the ester and the acid suggest that further ring formation has occurred during the pyrolysis of trimethylchebulic acid (I; R = Me). If the *iso*coumarin ring remains undisturbed, structure (X) may be advanced for the acid, $C_{16}H_{16}O_8$, but (XI), (XII), or (XIII) must be considered if the original lactone ring is ruptured during the pyrolysis. All attempts to decarboxylate the acid or to prepare benzylidene, *p*-nitrobenzylidene, piperonylidene, and *iso*nitroso-derivatives were unsuccessful, although the latter failures are not regarded as

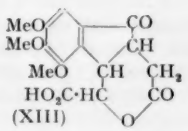

(IX)

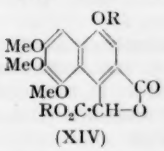

(X)


(XI)

excluding the presence of a keto-methylene group. The acid, $C_{16}H_{16}O_8$, was recovered after being heated with palladium–charcoal in boiling *p*-cymene, but it was dehydrogenated to $C_{16}H_{14}O_8$ by selenium dioxide. Unfortunately small amounts of material only were available and any conclusions must be regarded as provisional and requiring confirmation. But the properties of $C_{16}H_{14}O_8$ are consistent with the α-naphthol structure (XIV; R = H), which is derivable from the α-tetralone formula (XI) for the acid A, $C_{16}H_{16}O_8$. Thus in alkaline solution the acid $C_{16}H_{14}O_8$ gave a red azo-dye with benzenediazonium chloride, and on methylation with diazomethane gave a product $C_{18}H_{18}O_8$ which did not react with ketonic reagents and is regarded as (XIV; R = Me). The acid $C_{16}H_{14}O_8$ lost


(XII)


(XIII)


(XIV)

carbon dioxide on melting, but unfortunately the yellow resinous product could not be purified. The α-tetralone structure (XI) is also supported by the red colour shown by the amorphous 2 : 4-dinitrophenylhydrazone and by an infra-red spectroscopic study of the acid, $C_{16}H_{16}O_8$, its methyl ester, phenylhydrazone, and disodium salt made by Mr. H. J. V. Tyrrell to whom we are greatly indebted for the results in the annexed Table and their interpretation.

Infra-red absorption of the acid A, $C_{16}H_{16}O_8$ (*cm.*$^{-1}$).

	3-μ region	6-μ region				
Acid	No free OH band	1795	1742	1656	1587	1488
Me ester	,,	1789	1751	1684	1592	1488
Phenylhydrazone of ester	,,	1795	1751	Absent	1608	1492
Na_2 salt	Undissociated OH	Absent	Absent	1661	1621	1590

In the acid there were three bands which might reasonably be identified as carbonyl frequencies, *viz.*, 5·57, 5·74, and 6·04 μ. On esterification, the greatest change occurred in the band of lowest frequency, but since this disappeared from the spectrum of the phenylhydrazone of the ester it must be assigned to the ketonic-carbonyl group. This assignment is confirmed by the persistence of this band in the spectrum of the disodium salt. The frequency (1684 cm.$^{-1}$) of this band in the ester spectrum is the best guide to the nature of the ketonic group; it is too low for *cyclo*pentanone structures such as (X), (XII), (XIII), but fits well with that expected for the keto-group in structure (XI). Both the bands of higher frequency disappeared from the spectrum of the disodium salt, and must therefore be associated with the acid- and lactone-carbonyl groups. The band of highest frequency (1795 cm.$^{-1}$) can be assigned most plausibly to a γ-lactone structure (Grove and Willis, *loc. cit.*) as in (XI), leaving 1742 cm.$^{-1}$ as the acid-carbonyl frequency. Although this is unduly high for a solid dimeric acid, no unbonded-hydroxyl frequency was detected and these observations, together with the large shift of the keto-group frequency on passing from the acid to the ester, are not readily explicable at the moment.

When the acid $C_{16}H_{16}O_8$ was treated with thionyl chloride, it gave, in small yield, an acid chloride, m. p. 204—205°, but as the original acid, $C_{16}H_{16}O_8$, was not recoverable therefrom, some more profound structural change probably took place. Alkaline hydrolysis of the chloride gave an isomeric acid $C_{16}H_{16}O_8$, which separated with one molecule of water of crystallisation, and decomposition of the chloride with methyl alcohol gave a methyl ester, m. p. 227—228°, differing from the methyl ester, m. p. 149°, obtained by pyrolysis of trimethylchebulic acid. A satisfactory explanation cannot be advanced from the available evidence, but it is hoped to examine these reactions more fully in further work.

Experimental

Infra-red Spectra.—Substances were examined as mulls in Nujol. Spectra were obtained with a Grubb-Parsons S. 3*A* spectrometer.

Chebulinic Acid.—This has usually been isolated by extraction of powdered myrobalans with aqueous alcohol. The use of acetone (4·5 vols.) as a solvent was found advantageous. The acetone extract was concentrated to about one-seventh of its volume, diluted with seven volumes of water, and filtered from ellagic acid and other insoluble matter; the filtrate gradually deposited chebulinic acid, which was collected, washed with ether, and crystallised from water, forming needles (5—10%, varying with origin of the myrobalans).

Trimethylchebulic Acid (I; R = Me).—Isolation of chebulic acid as thallium salt (Freudenberg and Fick, *Ber.*, 1920, **53**, 1728; Schmidt, Heintzeler, and Mayer, *loc. cit.*) was tedious and Schmidt and Mayer's method (*loc. cit.*) of isolation of trimethylchebulic acid [Found : equiv. (cold), 132·0, (hot), 100·5. Calc. for $C_{17}H_{18}O_{11}$: equiv. (cold), 132·8; (hot), 99·6] was more satisfactory.

Trimethyl trimethylchebulate, prepared with diazomethane in ether–acetone, was a pale yellow oil, b. p. 200—205°/0·001 mm. (Found : C, 54·3; H, 5·7; OMe, 42·0. Calc. for $C_{20}H_{24}O_{11}$: C, 54·5; H, 5·5; OMe, 42·3%), which yielded trimethylchebulic triamide as prisms, m. p. 254—255° (decomp.) (Found : C, 51·8; H, 5·5; N, 10·8. Calc. for $C_{17}H_{21}O_8N_3$: C, 51·6; H, 5·3; N, 10·6%).

Fusion of Trimethylchebulic Acid with Potassium Hydroxide.—Trimethylchebulic acid (4·5 g.) was stirred with potassium hydroxide (30 g.) and water (15 c.c.); the temperature was raised to 100° in ½ hr., to 200° in the next ½ hr., and finally to 300° in the third ½ hr. The cooled melt was dissolved in water, acidified with concentrated hydrochloric acid, decolorised with charcoal, and extracted with ether. Removal of the ether left a brown residue which was taken up in hot water (50 c.c.), treated with charcoal, and filtered, and excess of calcium chloride was added. The insoluble calcium salt was decomposed with dilute sulphuric acid,

and the acid, isolated with ether, crystallised from water in needles (0·6 g.), m. p. 109°, undepressed on admixture with hydrated oxalic acid. The filtrate from the calcium oxalate was acidified and the acid, isolated with ether, separated from a little water in needles (0·51 g.), m. p. 185°, undepressed on admixture with succinic acid. The aqueous mother-liquors were evaporated to dryness and the residue was dissolved in methyl alcohol (5 c.c.) and mixed with ethereal diazomethane. After 12 hr. the solvent was removed and the residue distilled at 0·3 mm. (bath-temp. 155—165°). The distillate separated from methyl alcohol in prisms (0·1 g.), m. p. 82°, undepressed on admixture with methyl trimethylgallate, m. p. 82°, and converted into trimethylgallic acid, m. p. 167°, by alkaline hydrolysis.

*Propane-*1 : 1 : 2 : 3-*tetracarboxylic Acid.*—The tetramethyl ester (*Org. Synth.*, 1925, **4**, 29) was refluxed with excess of 2N-sodium hydroxide for 1½ hr. The solution was acidified and the *acid*, isolated with ether, crystallised from acetic acid in needles, m. p. 144—145° (decomp.) (Found : C, 38·3; H, 3·8. $C_7H_8O_8$ requires C, 38·2; H, 3·6%).

α-Dicarbamoylmethylsuccinimide (V).—A methyl-alcoholic solution of tetraethyl propane-1 : 1 : 2 : 3-tetracarboxylate was saturated with ammonia and heated in a sealed tube at 100° for 24 hr. Removal of the solvent and crystallisation of the residue from hot water gave the *diamide* as prisms, m. p. 244—245° (decomp.) (Found : C, 42·4; H, 4·7; N, 21·4. $C_7H_9O_4N_3$ requires C, 42·2; H, 4·5; N, 21·1%).

Triethyl Ethoxalyltricarballylate (VII).—Triethyl tricarballylate (13·7 c.c.) was added to diethyl oxalate (7·8 c.c.) and potassium ethoxide (from potassium, 2·25 g.) in ether (10 c.c.). After 24 hr. water was added and the aqueous extract was acidified and extracted with ether. Removal of the solvent gave a pale yellow oil which slowly deposited triethyl 4 : 5-dioxo*cyclo*pentane-1 : 2 : 3-tricarboxylate (VI) which separated from ethyl alcohol in prisms (0·35 g.), m. p. 122—123° (Found : C, 53·5; H, 5·9. Calc. for $C_{14}H_{18}O_8$: C, 53·5; H, 5·7%). Wislicenus and Schwanhausser (*loc. cit.*) and Gault (*loc. cit.*) give m. p. 122—123° and 127° respectively. The osazone separated from alcohol in yellow needles, m. p. 162—163° (Found : C, 63·3; H, 6·0; N, 11·1. Calc. for $C_{28}H_{30}O_6N_4$: C, 63·2; H, 6·1; N, 11·3%). Wislicenus and Schwanhausser (*loc. cit.*) give m. p. 162—163°. The *quinoxaline* derivative crystallised from aqueous alcohol in yellow elongated prisms, m. p. 170—171° (Found : C, 62·2; H, 5·7; N, 7·1. $C_{20}H_{22}O_6N_2$ requires C, 62·2; H, 5·7; N, 7·3%).

Triethyl ethoxalyltricarballylate (VII), on distillation at 1 mm., gave tetraethyl propane-1 : 1 : 2 : 3-tetracarboxylate, b. p. 160—162/1 mm. (Found : C, 54·0; H, 7·4. Calc. for $C_{15}H_{24}O_8$: C, 54·2; H, 7·4%), which was hydrolysed by alkali to the tetracarboxylic acid melting at 144—145° with loss of carbon dioxide and formation of tricarballylic acid, m. p. 157—159°. The *methyl ether* of (VII), prepared by diazomethane in ether–acetone, was a yellow viscous oil, b. p. 170—175°/0·1 mm. (Found : C, 54·2; H, 7·0. $C_{17}H_{26}O_9$ require C, 54·5; H, 7·0%).

γ-Lactone (III; R = OEt) *of Triethyl* 1-*Hydroxybutane-*1 : 2 : 3 : 4-*tetracarboxylate.*—The ester (VII) (10 g.) was reduced in alcohol at 100°/100 atm. with Raney nickel (1·5 g.) during 12 hr. After removal of the catalyst and solvent, the residue yielded the *lactone* (III; R = OEt) as a colourless oil, b. p. 176—178°/0·3 mm. (Found : C, 53·5; H, 6·6. $C_{14}H_{20}O_8$ requires C, 53·2; H, 6·3%), which gave the acid (III; R = OH) as a hygroscopic oil. The triamide was prepared from a methyl-alcoholic solution of the ester (III; R = OEt) which was saturated with ammonia at −10° and kept at room temperature for 4 days. Then after 1 hour's refluxing the *amide* was collected. It separated from water in prisms, m. p. 244—245° (decomp.) (Found : C, 42·1; H, 5·1; N, 18·2. $C_8H_{11}O_5N_3$ requires C, 41·9; H, 4·8; N, 18·3%). The ester (III; R = OEt) (1·65 g.) was heated on the steam-bath for 2 hr. with N-sodium hydroxide (40 c.c.), cooled to room temperature, and mixed with 2N-sodium hydroxide (80 c.c.) and potassium permanganate (7·53 g.) in water (250 c.c.). After 12 hr., more N-sodium hydroxide (40 c.c.) was added and the solution heated for 2 hr. at 100°. Excess of permanganate was destroyed with methyl alcohol, the manganese dioxide was collected and washed with hot water, the concentrated filtrate and washings were acidified with acetic acid, and calcium chloride was added. The calcium oxalate was collected, washed, and dried at 110° (1·97 g.).

Pyrolysis of Trimethylchebulic Acid (I; R = Me).—The acid (I; R = Me) (7·6 g.) was heated with freshly precipitated copper powder (2·5 g.) at 260—290°/0·5 mm. The red sublimate (3 g.) was heated at 100° for 2 hr. with 2N-sodium hydroxide (30 c.c.) and, after acidification with 2N-sulphuric acid, tarry impurities were removed by filtration and the orange filtrate was extracted with ether for 48 hr. The ether was removed, and the residue was taken up in acetone (100 c.c.), mixed with excess of ethereal diazomethane, and after 12 hr. filtered and evaporated. The residual oil was distilled. The small fraction (Y) (0·2 g.) boiling below

150°/0·005 mm. was hydrolysed with sodium hydroxide, and the acid, isolated by continuous extraction with ether, gave the succinic acid reaction with resorcinol. The yellow viscous fraction (1·7 g.) of b. p. 204—208°/0·003 mm. yielded a colourless solid (A) when triturated with ether. The residual liquors were evaporated and the orange syrup (1·3 g.) was poured in benzene–light petroleum (b. p. 40—60°) (3 : 1; 150 c.c.) on to a charcoal column (2·5 × 14·5 cm.) and eluted (100-c.c. fractions). The preceding mixture (5 × 100 c.c.) removed a yellow oil. Benzene (fractions 6—10) removed ester A (see below). Benzene–ether (9 : 1) (fractions 11—18) removed a semi-solid material, whence fractional crystallisation from methyl alcohol afforded esters A and B. Benzene–ether (4 fractions, 3 : 1; 2 fractions, 1 : 1) removed oils. Ether and ether–acetone (9 : 1) (2 fractions each) removed nothing. Finally ether–acetone (1 : 1; fractions 29—35) removed the *iso*coumarin ester (IX; R = Me).

5 : 6 : 7-*Trimethoxy*iso*coumarin*-3-*carboxylic Acid* (IX; R = H).—Fractions 29—35 of the preceding separation, when combined and crystallised from methyl alcohol, gave *methyl* 5 : 6 : 7-*trimethoxy*iso*coumarin*-3-*carboxylate* (IX; R = Me) as needles (0·1 g.), m. p. 154—155° (Found : C, 57·2; H, 4·6. $C_{14}H_{14}O_7$ requires C, 57·2; H, 4·9%), undepressed on admixture with a synthetic specimen (see following paper). This ester (0·05 g.), refluxed for 4 hr. with 2N-sulphuric acid (4 c.c.) and acetic acid (1 c.c.), gave its *acid* (IX; R = H), needles (from alcohol), m. p. 262—264° (Found : C, 55·9; H, 4·4. $C_{13}H_{12}O_7$ requires C, 55·7; H, 4·3%), undepressed on admixture with a synthetic specimen.

The *chloride*, prepared from the acid (IX; R = H) and thionyl chloride (5 vols.), crystallised from benzene in needles, m. p. 163—164° (Found : C, 52·6; H, 3·7. $C_{13}H_{11}O_6Cl$ requires C, 52·3; H, 3·7%), and gave the *ethyl* ester (IX; R = Et), needles (from alcohol, m. p. 118° (Found : C, 58·5; H, 5·3. $C_{15}H_{16}O_7$ requires C, 58·4; H, 5·2%).

Ethyl 3 : 4-*Dihydro*-5 : 6 : 7-*trimethoxy*iso*coumarin*-3-*carboxylate*.—A solution of ethyl 5 : 6 : 7-trimethoxy*iso*coumarin-3-carboxylate (IX; R = Et) (1 g.) in glacial acetic acid (25 c.c.) was reduced at 50° in presence of 30% palladium–charcoal (0·1 g.), this requiring 48 hr. for completion. The reduced *ester* was distilled at 250° (bath)/0·1 mm. and then crystallised from alcohol in prisms, m. p. 84—85° (Found : C, 57·8; H, 5·9. $C_{15}H_{18}O_7$ requires C, 58·1; H, 5·8%), identical with a synthetic specimen described in the following paper. This ester was recovered after attempted dehydrogenation with 30% palladium–charcoal in boiling *p*-cymene.

The Optically Active Acid, $C_{16}H_{16}O_8$ (XI).—The ester (A) (0·5 g.) obtained by trituration with ether (above) was combined with fractions 6—10 (0·1 g.) and crystallised from methyl alcohol; the *methyl* ester (A) was obtained in prisms (0·5 g.), m. p. 149°, $[\alpha]_D^{20}$ +238° (*c*, 2·78 in $CHCl_3$) [Found : *M* (Rast), 345; C, 58·2; H, 5·1. $C_{17}H_{18}O_8$ requires *M*, 350; C, 58·3; H, 5·1%]. A further crop (0·05 g.), m. p. 149°, was obtained from the less soluble portions on fractionation of the combined fractions 11—18 from methyl alcohol. The *acid*, $C_{16}H_{16}O_8$ (XI), prepared by hydrolysis of methyl ester (A) by 2 hours' boiling with 2N-hydrochloric acid or methyl-alcoholic 3% potassium hydroxide, separated from hot water in rhombic prisms, m. p. 217°, $[\alpha]_D^{20}$ +221° (*c*, 1·36 in MeOH) [Found : equiv. (cold), 334, (hot), 168·5; C, 57·2; H, 4·8. $C_{16}H_{16}O_8$ requires equiv. (cold), 336, (hot), 168·5; C, 57·2; H, 4·8%]. Attempts to reduce it, to dehydrogenate it in presence of palladium or platinum catalysts, and to decarboxylate it with copper catalysts were unsuccessful. Oxidation of the acid (XI) with potassium ferricyanide (cf. *J.*, 1951, 3511) gave 3 : 4 : 5-trimethoxyphthalic acid, identified as anhydride, m. p. 144°, and *N*-methylimide, m. p. 127°. A methyl ester, m. p. 149°, identical with methyl ester (A), was prepared by the action of methyl-alcoholic hydrogen chloride or diazomethane on the acid (XI).

The *phenylhydrazone* of the methyl ester separated from methyl alcohol in hexagonal prisms, m. p. 197—198° (Found : C, 62·6; H, 5·5; N, 6·3. $C_{23}H_{24}O_7N_2$ requires C, 62·7; H, 5·5; N, 6·4%). The p-*nitrobenzyl* ester, prepared by refluxing the acid (XI) (0·1 g.) in 1 mol. of N-sodium hydroxide for 1 hr. with *p*-nitrobenzyl bromide (0·067 g.) in alcohol, crystallised from aqueous alcohol in prisms, m. p. 122—123° (Found : C, 58·4; H, 4·5; N, 2·7. $C_{23}H_{21}O_{10}N$ requires C, 58·6; H, 4·5; N, 3·0%). The methyl ester (0·27 g.) was added to methyl alcohol (5 c.c.) saturated with ammonia at 10°; after 48 hr. at room temperature, propyl alcohol (5 c.c.) was added and the solution refluxed for 2 hr., after which the solvent was removed and the *amide* crystallised from water in prisms, m. p. 232—234° (decomp.) (Found : C, 57·2; H, 5·1; N, 4·2. $C_{16}H_{17}O_7N$ requires C, 57·3; H, 5·1; N, 4·2%).

Dehydrogenation of the Acid (XI) *with Selenium Dioxide*.—A solution of the acid (XI) (0·11 g.) and selenium dioxide (0·02 g.) in water (15 c.c.) was refluxed for 4 hr. The precipitated selenium was collected, and the *acid* which separated from the filtrate on cooling crystallised from glacial acetic acid in needles (0·05 g.), m. p. 210°, $[\alpha]_D^{20}$ +52·5° (*c*, 0·45 in methanol) (Found :

C, 57·2; H, 4·4. $C_{16}H_{14}O_8$ requires C, 57·5; H, 4·2%). The *methyl* ester, prepared by diazomethane, separated from methyl alcohol in elongated plates, m. p. 147° (Found: C, 59·4; H, 5·0. $C_{18}H_{18}O_8$ requires C, 59·7; H, 5·0%).

Action of Thionyl Chloride on the Acid (XI).—After the acid (XI) had been refluxed with excess of thionyl chloride for 30 min., the excess of thionyl chloride was removed and benzene added. The *acid chloride* which separated crystallised from benzene–light petroleum (b. p. 40—60°) in plates, m. p. 204—205° (decomp.) (Found: C, 54·2; H, 3·8. $C_{16}H_{15}O_7Cl$ requires C, 54·2; H, 4·2%). It was warmed with dilute sodium hydroxide until dissolution was complete; acidification gave an *acid*, which crystallised from aqueous alcohol in long needles, m. p. 198° (decomp.) (Found: C, 54·5; H, 5·3. $C_{16}H_{16}O_8,H_2O$ requires C, 54·2; H, 5·1%). The *methyl* ester, prepared by decomposition of the acid chloride with methyl alcohol, separated from methyl alcohol in needles, m. p. 227—228°, $[\alpha]_D^{20}$ +164 (*c*, 1·07 in MeOH) (Found: C, 58·5; H, 5·4. $C_{17}H_{18}O_8$ requires C, 58·3; H, 5·1%). The *ethyl* ester, prepared similarly in ethyl alcohol, crystallised in needles, m. p. 142° (Found: C, 59·4; H, 5·7. $C_{18}H_{20}O_8$ requires C, 59·3; H, 5·5%).

The Optically Inactive Methyl Ester (*B*).—This *product*, obtained from the more soluble portions during crystallisation of the combined fractions 11—18, separated from methyl alcohol in prisms (0·07 g.), m. p. 141°, $[\alpha]_D^{20}$ 0° (*c*, 0·38 in MeOH) (Found: C, 58·2; H, 5·1. $C_{17}H_{18}O_8$ requires C, 58·3; H, 5·1%), depressed to 110—113° on admixture with methyl ester (A). The *phenylhydrazone* crystallised from acetic acid in needles, m. p. 214° (Found: C, 62·5; H, 5·5; N, 6·4. $C_{23}H_{24}O_7N_2$ requires C, 62·7; H, 5·5; N, 6·4%), and the 2 : 4-*dinitrophenylhydrazone* crystallised from the same solvent in orange needles, m. p. 233—234° (Found: C, 51·9; H, 4·0; N, 10·7. $C_{23}H_{22}O_{11}N_4$ requires C, 52·1; H, 4·2; N, 10·6%).

Our thanks are offered to the Government of Ceylon for the award of a scholarship to one of us, and to the Imperial Chemical Industries Limited for a grant towards the expenses of the research.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, June 12th*, 1954.]

Chebulinic Acid. Part III. Oxidation of Ellagic and Flavellagic Acids and the Synthesis of Some* iso*Coumarin Derivatives.*

By R. D. HAWORTH, H. K. PINDRED, and (in part) P. R. JEFFERIES.

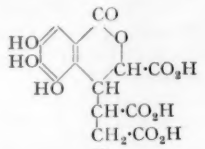
[Reprint Order No. 5462.]

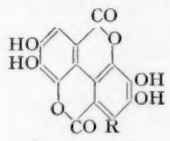
Whilst the oxidation of ellagic acid with hydrogen peroxide yields simple aliphatic compounds, flavellagic acid gives 20% yields of 5 : 6 : 7-trihydroxy-4-*iso*coumarinylacetic acid (III; R = R′ = H). Decarboxylation of the trimethyl ether afforded 5 : 6 : 7-trimethoxy-4-methyl*iso*coumarin, which was identified by comparison with a synthetic product. Although a synthesis of the 4-acetic acid (III; R = R′ = H) has not been realised, a number of synthetic 5 : 6 : 7-trimethoxy*iso*coumarin derivatives substituted in the 3- and the 4-position, and related to chebulic acid, flavellagic acid, and galloflavin, have been prepared.

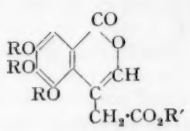
SCHMIDT AND MAYER (*Annalen*, 1951, **571**, 1) suggested that chebulic acid (I) represented an oxidation product of ellagic acid (II; R = H), and the present paper is a result of experiments aiming at the oxidative disruption of one of the phenolic nuclei of ellagic acid by means of hydrogen peroxide. Difficulties were encountered in the reactions; at room temperature little or no oxidation occurred and at higher temperatures a very complex mixture of relatively simple aliphatic acids resulted, which gave no clue to the nature of the break-down. The acid mixtures were methylated, and fractional distillation of the esters and subsequent hydrolysis of the fractions gave oxalic, malonic, succinic, and ethane-1 : 2 : 2-tricarboxylic acid, and intractable oils. In view of the difficulty of isolating phenolic acid oxidation products our attention was diverted to the peroxide oxidation of flavellagic acid (II; R = OH). This proceeded smoothly in alkaline solution at room

* Part II, preceding paper.

temperature, giving 20% yields of a phenolic acid, $C_{11}H_8O_7$, which was subsequently shown to be 5 : 6 : 7-trihydroxy-4-*iso*coumarinylacetic acid (III; R = R′ = H). Methylation with diazomethane yielded the dimorphous ether-ester (III; R = R′ = Me) and thence the ether-acid (III; R = Me, R′ = H) on hydrolysis and a 3 : 4-dihydro-derivative on catalytic reduction. The acid (III; R = Me, R′ = H) titrated in the cold as a monobasic

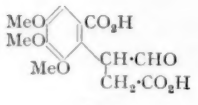

(I)

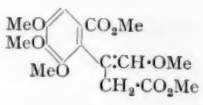

(II)

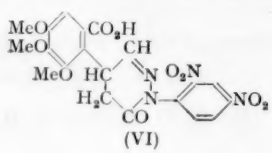

(III)

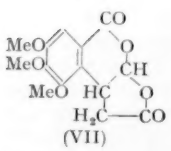
acid, but the lactone ring was ruptured by warm alkali and acidification then yielded β-(6-carboxy-2 : 3 : 4-trimethoxyphenyl)-β-formylpropionic acid (IV), a dibasic acid which was reconverted into 5 : 6 : 7-trimethoxy-4-*iso*coumarinylacetic acid (III; R = Me, R′ = H) only after prolonged boiling with mineral acids. The dibasic acid (IV) was oxidised by potassium ferricyanide to 3 : 4 : 5-trimethoxyphthalic acid, thus proving that the pyrogallol nucleus of the flavellagic acid (II; R = OH) remained intact during the oxidation, and on methylation with diazomethane it was converted into either the dimethyl ester or the *O*-enol ether (V) according to the conditions; both derivatives yielded the same 2 : 4-dinitrophenylhydrazone. This evidence for a carbonyl group was confirmed by the production of a 2 : 4-dinitrophenylhydrazone, of structure (VI), from the dibasic acid (IV). Sublimation of the dibasic acid (IV) yielded a dilactone (VII) which was stable to boiling water or alcohol and unattacked by diazomethane or ketonic reagents, and was reconverted into the dibasic acid (IV) by hydrolysis with sodium hydroxide.

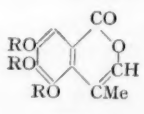
5 : 6 : 7-Trimethoxy-4-*iso*coumarinylacetic acid (III; R = Me, R′ = H) was decarboxyl-

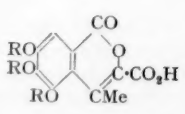

(IV)


(V)


(VI)


(VII)

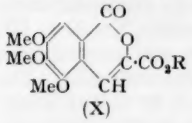

(VIII)

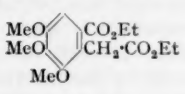

(IX)

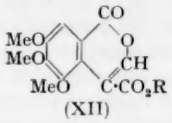
ated by copper at 300°, and the product was identified by a comparison with a synthetic specimen as 5 : 6 : 7-trimethoxy-4-methyl*iso*coumarin (VIII; R = Me). A synthesis of 5 : 6 : 7-trihydroxy-4-methyl*iso*coumarin (VIII; R = H) has been reported by Fritsch (*Ber.*, 1893, **26**, 421) but the analytical results given are poor. Chloroacetone reacted with potassium gallate, and the resulting acetonyl gallate (gallacetol) was converted by 80% sulphuric acid into 5 : 6 : 7-trihydroxy-4-methyl*iso*coumarin (VIII; R = H) which gave the trimethyl ether (VIII; R = Me) with diazomethane. Acetonyl 3 : 4 : 5-trimethoxybenzoate, which was obtained from chloroacetone and 3 : 4 : 5-trimethoxybenzoic acid, could, however, not be cyclised to (VIII; R = Me). The isolation of 4-methyl*iso*coumarin (VIII; R = Me) can be accounted for on the basis of structure (III) or (IX) for the oxidation product of flavellagic acid. Of these, only (III) provides a satisfactory explanation of the reactions summarised above, and (IX) is also excluded by spectroscopic evidence. The ultra-violet absorption curves of 5 : 6 : 7-trimethoxy-4-*iso*coumarinylacetic acid (III; R = Me, R′ = H) and 5 : 6 : 7-trimethoxy-4-methyl*iso*coumarin (VIII; R = Me) were almost superposable with peaks at 2450 (log ε 4·48) and 3300 Å (log ε 3·50), whilst the maximum for 5 : 6 : 7-trimethoxy*iso*coumarin-3-carboxylic acid (X; R = H), synthe-

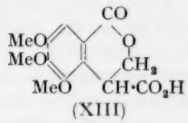
sised by the method described on p. 3620, at 2580 Å (log ε 4·52), indicated the presence of a more conjugated chromophoric system in the latter acid.

Although the structure of the oxidation product of flavellagic acid is firmly established as (III; R = R′ = H) from the evidence outlined above, synthetical evidence has been sought, but, so far, without success. Ethyl 6-ethoxycarbonyl-2 : 3 : 4-trimethoxyphenylacetate (XI) was prepared from 4 : 5 : 6-trimethoxy-3-trichloromethylphthalide (Alimchandani, *J.*, 1924, **125**, 540) by Meldrum and Parikh's method (*J. Proc. Ind. Acad. Sci.*, 1934—1935, **1**, 430), and with ethyl formate in presence of potassium ethoxide afforded, after cyclisation, ethyl 5 : 6 : 7-trimethoxy*iso*coumarin-4-carboxylate (XII; R = Et).


(X)

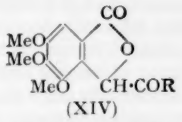

(XI)

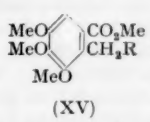

(XII)

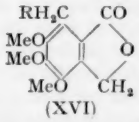

(XIII)

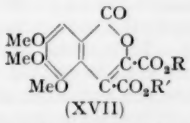
Hydrolysis to the acid (XII; R = H) could not be brought about with acids, alkalis, or boron trifluoride in acetic acid, and consequently Arndt–Eistert ascent to (III; R = Me, R′ = H) was excluded. As this difficulty in hydrolysis might have been due to the production of unstable β-aldehydic ester intermediate products, the ester (XII; R = Et) was reduced to its 3 : 4-dihydro-derivative which was readily hydrolysed by acids to 3 : 4-dihydro-5 : 6 : 7-trimethoxy*iso*coumarin-4-carboxylic acid (XIII) in which the lactone ring was readily ruptured by boiling water. Unfortunately the chloride of the acid (XIII) could not be prepared; reaction with thionyl chloride gave a sulphur-containing oil, which could not be converted into the methyl ester or the diazo-ketone by treatment with methyl alcohol or diazomethane respectively. This failure to prepare an acid chloride from (XII; R = H) or (XIII) is peculiar; as will be seen later (p. 3620) no such difficulties were encountered with the isomeric 5 : 6 : 7-trimethoxy*iso*coumarin-3-carboxylic acid (X; R = H) or its 3 : 4-dihydro-derivative, and 4 : 5 : 6-trimethoxyphthalide-3-carboxylic acid (XIV; R = OH) (Bargellini and Molina, *Atti R. Accad. Lincei*, 1912, **21**, II, 146) was readily converted *via* its acid chloride and diazo-ketone into 3-acetyl-4 : 5 : 6-trimethoxyphthalide (XIV; R = Me), identical with the compound prepared from galloflavin (Haworth and McLachlan, *J.*, 1952, 1583).

A synthesis of (III; R = Me, R′ = H) based on 2 : 3 : 4-trimethoxy-6-methoxycarbonylbenzyl cyanide (XV; R = CN) was envisaged but attempts to prepare this ester from methyl 2-chloromethyl-3 : 4 : 5-trimethoxybenzoate (XV; R = Cl) (Haworth, Moore, and Pauson, *J.*, 1949, 3278) gave results which showed that the product obtained by chloromethylation of methyl 3 : 4 : 5-trimethoxybenzoate was 7-chloromethyl-4 : 5 : 6-trimethoxyphthalide (XVI; R = Cl) and not (XV; R = Cl) as previously suggested. Thus treatment with potassium cyanide gave 7-cyanomethyl-4 : 5 : 6-trimethoxyphthalide (XVI; R = CN), which had lactonic properties and on alkaline hydrolysis gave the corresponding lactonic acid (XVI; R = CO_2H). In addition, alkaline hydrolysis of 7-chloromethylphthalide (XVI; R = Cl) gave, not 4 : 5 : 6-trimethoxyphthalide which would be expected from earlier theoretical views, but 7-hydroxymethylphthalide (XVI; R = OH) which contained a lactone ring and gave a positive Zerewitinoff test. The need for this structural revision was also proved by the preparation of 7-chloromethylphthalide (XVI; R = Cl) by the action of formaldehyde and hydrochloric acid on 4 : 5 : 6-trimethoxyphthalide.


(XIV)


(XV)


(XVI)


(XVII)

Attempts were also made to synthesise (III) or its derivatives by extensions of the *iso*coumarin synthesis used by Fritsch (*loc. cit.*; *Friedländer*, 1890—1894, **3**, 970). The first attempt failed because ethyl γ-chloroacetoacetate (Alexandrow, *Ber.*, 1913, **46**, 1022)

could not be condensed with potassium or silver gallate. A second scheme had for its objective the synthesis of 5 : 6 : 7-trihydroxy-4-propyl*iso*coumarin, which could probably have been made from (III). A convenient method of preparation of chloromethyl propyl ketone, from butyryl chloride *via* the corresponding diazo-ketone, is described in the Experimental section, but although satisfactory reaction with potassium gallate to 2-oxopentyl 3 : 4 : 5-trihydroxybenzoate was realised, we were unable to convert this ester into an *iso*coumarin derivative.

Condensation of the homophthalic ester (XI) with ethyl oxalate in presence of potassium ethoxide gave a product which readily cyclised to diethyl 5 : 6 : 7-trimethoxy*iso*coumarin-3 : 4-dicarboxylate (XVII; R = R′ = Et). This ester was hydrolysed by dilute sulphuric acid in acetic acid to 5 : 6 : 7-trimethoxy*iso*coumarin-3-carboxylic acid (X; R = H), m. p. 262—264°. An acid ester, probably (XVII; R = H, R′ = Et), was isolated from some experiments, and converted into (X; R = H) by further treatment with acid. The decarboxylation observed during hydrolysis of the ester (XVII; R = R′ = Et) would be expected on theoretical grounds to result in the elimination of the 4-ethoxycarbonyl group, and Vorozhtsov and Bogusevich (*Zhur. Obshchey Khim.*, 1940, **10**, 2014) have shown that diethyl *iso*coumarin-3 : 4-dicarboxylate was converted into *iso*coumarin-3-carboxylic acid by hot concentrated hydrochloric acid. The constitution assigned to the trimethoxy*iso*coumarin-3-carboxylic acid was finally established by preparation of the ethyl ester, m. p. 118°, which differed from ethyl 5 : 6 : 7-trimethoxy*iso*coumarin-4-carboxylate (XII; R = Et), m. p. 106°, described previously. Tschitschibabin, Kirssanow, Korolew, and Woroschzow (*Annalen*, 1929, **469**, 93) prepared 5 : 6 : 7-trimethoxy*iso*-coumarin-3-carboxylic acid (X; R = H) by oxidation of bergenin, but the melting point reported is 10° lower than that of the synthetic sample prepared as above, although the melting point of their ester is in good agreement with that of the ester prepared from our acid (X; R = H).

The identity of 5 : 6 : 7-trimethoxy*iso*coumarin-3-carboxylic acid (X; R = H) with the acid obtained by pyrolysis of trimethylchebulic acid (see previous paper, p. 3612) was established by direct comparison of the acids, acid chlorides, and methyl and ethyl esters, and of the 3 : 4-dihydro-acids and their ethyl esters. 5 : 6 : 7-Trimethoxy*iso*coumarin-3-carboxylic acid (X; R = H), unlike the 4-isomer, readily gave an acid chloride, which with diazomethane gave 3-diazoacetyl-5 : 6 : 7-trimethoxy*iso*coumarin. The diazo-compound was converted by Wolff rearrangement with silver oxide in methyl alcohol into methyl 5 : 6 : 7-trimethoxy-3-*iso*coumarinylacetate; the yields were poor, and the product, m. p. 127—128°, was not identical with either of the dimorphous forms of the 4-isomer (III; R = R′ = Me) prepared from flavellagic acid.

Experimental

Oxidation of Ellagic Acid (II; R = H).—Hydrogen peroxide (62·5 c.c. of 100-vol.) was added dropwise and with stirring to a solution of ellagic acid (10 g.) in water containing sodium hydroxide (7 g.) at 90—95°. The ice-cooled red solution was saturated with sulphur dioxide, and after 3 hr. unchanged ellagic acid (3 g.) was collected; the pale yellow filtrate, extracted continuously with ether for 2 days, gave a brown oil. This oil (17 g.; obtained from several experiments) was dissolved in acetone (100 c.c.) and mixed with ethereal diazomethane (from 60 g. of nitrosomethylurea), and after 18 hr. the residual brown oil (20 g.) was fractionated at 0·5 mm., yielding fractions, (1) (4·8 g.) b. p. 40—47°/0·5 mm., (2) (4·7 g.) b. p. 92—100°/0·5 mm., and (3) (3·1 g.), b. p. 120—130°/0·5 mm., and a residue.

Fraction (1) (2 g.) was hydrolysed for 2 hr. with warm methyl-alcoholic 10% potassium hydroxide (50 c.c.). Water (100 c.c.) was added, the alcohol was removed, and the acidified solution after continuous extraction with ether for 1 day gave a colourless oil which was taken up in a little water and treated with excess of calcium chloride solution. The precipitated calcium oxalate yielded hydrated oxalic acid, m. p. 100—101°. The filtrate from the calcium oxalate was extracted with ether for 1 day, yielding a solid, m. p. 120—130° (Found : equiv., 55), which when heated with benzaldehyde (2 c.c.), pyridine (5 c.c.), and piperidine (2 drops) gave cinnamic acid (1·1 g.), m. p. 133°. The filtrate therefrom was rendered alkaline, and the neutral and the basic products were removed with ether; acidification, continuous ether-extraction for 18 hr., and sublimation then yielded succinic anhydride, m. p. 119° (from benzene).

Fraction (2) was largely trimethyl ethane-1 : 2 : 2-tricarboxylate, b. p. 98—102°/0·5 mm. [Found : C, 45·8; H, 6·1; OMe, 40·5. $C_5H_3O_3(OMe)_3$ requires C, 46·5; H, 5·9; OMe, 45·5%]. Hydrolysis with methyl-alcoholic potassium hydroxide gave the acid, which was isolated with ether and crystallised from ethyl acetate in prisms, m. p. 156—157° (Found : equiv., 53·5; C, 37·4; H, 3·8%. Calc. for $C_5H_6O_6$: equiv., 54·0; C, 37·0; H, 3·7%), undepressed on admixture with a specimen prepared as described by Kay and Perkin (*J.*, 1906, **89**, 1643).

Fraction (3) (Found : C, 48·9; H, 5·1. Calc. for $C_{10}H_{12}O_7$: C, 49·2; H, 4·9%) gave an intractable hygroscopic oil on hydrolysis.

Flavellagic Acid (II; R = OH).—When prepared by persulphate oxidation of gallic acid as described by Perkin (*J.*, 1906, **89**, 251) and purified by hydrolysis of the penta-acetyl derivative, this had m. p. 317—319°.

Oxidation of Flavellagic Acid.—Hydrogen peroxide (15 c.c. of 100-vol.) was gradually added with stirring to a solution of flavellagic acid (16 g.) in 4% aqueous potassium hydroxide (600 c.c.). The temperature rose to 38°, after which oxidation was allowed to proceed, without stirring, at room temperature for 7 hr. The solution was acidified and after 2 hr. unchanged flavellagic acid (4 g.) was collected. The red filtrate gave, after continuous ether-extraction for 2 days, a red oil (5 g.) and a pale yellow solid (2·5 g.). The oil, with ethereal diazomethane, yielded an ester, b. p. <130°/0·2 mm., but was not investigated further. The solid was crystallised from hot water and gave the *monohydrate* of 5 : 6 : 7-*trihydroxy*-4-iso*coumarinylacetic acid* (III; R = R′ = H) as colourless needles (2·0 g.), m. p. 280—290° (decomp.) (Found, after drying in a vacuum for 1 day : C, 48·8; H, 3·7. $C_{11}H_8O_7,H_2O$ requires C, 48·8; H, 3·7%), which gave a deep blue ferric test. The *anhydrous acid* (III; R = R′ = H) was obtained by 6 hours' drying at 130°/0·2 mm. over phosphoric oxide (Found : C, 52·4; H, 3·5. $C_{11}H_8O_7$ requires C, 52·3; H, 3·2%).

Methyl 5 : 6 : 7-*Trimethoxy*-4-iso*coumarinylacetate* (III; R = R′ = Me).—To an acetone solution of the phenolic acid (III; R = R′ = H) (2 g.) was added excess of ethereal diazomethane (from 20 g. of nitrosomethylurea), and removal of the solvent after 12 hr. gave an oil which crystallised from methyl alcohol. The crystals (2·2 g.) were dimorphous; rapid separation from hot methyl alcohol gave needles, m. p. 122—123°, and slow crystallisation afforded rhombic prisms, m. p. 125—126° [Found : C, 58·2; H, 5·2; OMe, 40·0. $C_{11}H_4O_3(OMe)_4$ requires C, 58·4; H, 5·2; OMe, 40·4%]. This ester gave a negative Zerewitinoff test.

5 : 6 : 7-*Trimethoxy*-4-iso*coumarinylacetic Acid* (III; R = Me, R′ = H).—The foregoing ester (1 g.) was refluxed with concentrated hydrochloric acid (50 c.c.) and water (150 c.c.) for 1½ hr. The *acid* which separated on cooling crystallised from hot water or methyl alcohol in needles (0·8 g.), m. p. 210—211° (Found : equiv., 292; C, 57·3; H, 4·8%. $C_{14}H_{14}O_7$ requires equiv., 294; C, 57·1; H, 4·8%). The acid was reconverted into the methyl ester by refluxing with methyl alcohol and sulphuric acid. The *acid chloride*, prepared by refluxing with thionyl chloride (5 parts) for ½ hr., crystallised from benzene or toluene in prisms, m. p. 124—125° (Found : C, 53·7; H, 4·3. $C_{14}H_{13}O_6Cl$ requires C, 53·75; H, 4·3%). The *ethyl* ester (III; R = Me, R′ = Et), prepared from the chloride, separated from alcohol in needles, m. p. 138—139° (Found : C, 59·7; H, 5·7. $C_{16}H_{18}O_7$ requires C, 59·6; H, 5·6%. The *amide*, prepared by the action of dry ammonia on a benzene solution of the chloride, crystallised from water in needles, m. p. 230—231° (Found : C, 57·5; H, 5·2; N, 4·7. $C_{14}H_{15}O_6N$ requires C, 57·3; H, 5·1; N, 4·8%).

5 : 6 : 7-*Trimethoxy*iso*carbostyril*-4-*acetic Acid.*—The lactonic acid (III; R = Me, R′ = H) (0·65 g.) was treated in a sealed tube with a saturated solution (15 c.c.) of methyl-alcoholic ammonia for 18 hr. at 100°. Evaporation under reduced pressure gave a white solid which was taken up in water (10 c.c.) and acidified; the iso*carbostyril acid* crystallised from acetic acid in needles, m. p. 242—244° (Found : C, 57·0; H, 5·3; N, 4·8. $C_{14}H_{15}O_6N$ requires C, 57·3; H, 5·1; N, 4·8%).

3 : 4-*Dihydro*-5 : 6 : 7-*trimethoxy*-4-iso*coumarinylacetic Acid.*—A solution of methyl 5 : 6 : 7-trimethoxy-4-*iso*coumarinylacetate (III; R = R′ = Me) (0·9 g.) in acetic acid (30 c.c.) was reduced in presence of 25% palladium–charcoal (0·90 g.) at 50°. After 6 hr., the filtered solution yielded a pale yellow oil, b. p. 215—220° (bath)/0·1 mm., which solidified and crystallised from methyl alcohol in prisms, m. p. 74—75° (Found : C, 58·2; H, 5·8. $C_{15}H_{18}O_7$ requires C, 58·1; H, 5·8%). Hydrolysis of this *methyl* ester with 6% aqueous potassium hydroxide (30 parts) for 2 hr. yielded the *acid*, which separated from hot water in prisms, m. p. 177—178° (Found : C, 56·6; H, 5·5. $C_{14}H_{16}O_7$ requires C, 56·7; H, 5·4%). Methylation with methyl alcohol and sulphuric acid gave the methyl ester, m. p. 74—75°.

β-(6-*Carboxy*-2 : 3 : 4-*trimethoxyphenyl*)-β-*formylpropionic Acid* (IV).—The ester (III;

R = R′ = Me) (1 g.) was refluxed for 2 hr. with methyl-alcoholic 5% potassium hydroxide (40 c.c.). After removal of the alcohol and acidification, the dibasic *acid* (IV) was collected and crystallised from hot water; rhombic prisms (0·7 g.), m. p. 167—169° (decomp.) [Found : equiv., C, 53·7; H, 5·1; OMe, 29·8%. $C_{11}H_7O_5(OMe)_3$ requires equiv., 156; C, 53·8; H, 5·1; OMe, 29·8%], were obtained. The dibasic acid (IV) was converted into 5 : 6 : 7-trimethoxy-4-*iso*coumarinylacetic acid (III; R = Me, R′ = H), m. p. 210—211°, by 5 hours' heating with concentrated hydrochloric acid (14 parts) and water (46 parts). The acid (IV) was oxidised with potassium ferricyanide in the usual way; 3 : 4 : 5-trimethoxyphthalic acid was isolated and identified as the anhydride, m. p. 144°, and *N*-methylimide, m. p. 127°. The acid (IV) gave a 2 : 4-*dinitrophenylhydrazone* (VI) which crystallised from acetic acid in pale yellow needles, m. p. 281—282° (Found : C, 50·7; H, 3·8; N, 11·7. $C_{20}H_{18}O_{10}N_4$ requires C, 50·7; H, 3·8; N, 11·8%), and dissolved in cold sodium hydrogen carbonate solution. The *dimethyl* ester of the acid (IV), prepared by reaction with a small excess of ethereal diazomethane for ½ hr., was an oil, b. p. 220—225° (bath)/0·1 mm., yielding a 2 : 4-*dinitrophenylhydrazone*, which crystallised from methyl alcohol in deep yellow needles, m. p. 123° (Found : C, 51·0; H, 4·7; N, 10·7. $C_{22}H_{22}O_{11}N_4$ requires C, 51·0; H, 4·3; N, 10·8%). The *methyl ether* (V) of the enolic form of the above dimethyl ester, was obtained by treating the dibasic acid (IV) with excess of diazomethane for 24 hr.; it crystallised from methyl alcohol in stout prisms, m. p. 78—79° (Found : C, 57·3; H, 6·2. $C_{17}H_{22}O_8$ requires C, 57·6; H, 6·2%), which slowly reacted with 2 : 4-dinitrophenylhydrazine yielding the 2 : 4-dinitrophenylhydrazone of m. p. 123° described above.

The Dilactone (VII) *of* β-(6-*Carboxy*-2 : 3 : 4-*trimethoxyphenyl*)-β-*formylpropionic Acid*.—This was prepared by heating the acid (IV) either (*a*) at 175°/0·5 mm. or (*b*) with acetic anhydride (10 vol.) for 40 hr. The *dilactone* crystallised from hot water or benzene–light petroleum (b. p. 60—80°) in needles, m. p. 139—140° [Found : equiv., 145·5; C, 56·9; H, 4·8; OMe, 32·4%. $C_{11}H_5O_4(OMe)_3$ requires equiv., 147; C, 57·1; H, 4·8; OMe, 31·6%], which did not react with diazomethane but on alkaline hydrolysis regenerated the acid (IV), m. p. 167—169° (decomp.).

Decarboxylation of 5 : 6 : 7-*Trimethoxy*-4-iso*coumarinylacetic Acid* (IV; R = Me, R′ = H).—The lactonic acid (IV; R = Me, R′ = H) (1 g.) was heated for 1 hr. with copper powder at 280—300°. Distillation at 13 mm. yielded a small quantity of yellow oil, which gradually solidified and crystallised from methyl alcohol in colourless needles (0·1 g.), m. p. 93—94° (Found : C, 62·7; H, 5·8. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%), undepressed on admixture with a synthetic specimen of 5 : 6 : 7-*trimethoxy*-4-*methyl*iso*coumarin* (VIII; R = Me) (see below).

Acetonyl Gallate (*Gallacetol*).—A mixture of chloroacetone (9·2 c.c.), gallic acid (18·8 g.), potassium carbonate (6·8 g.), water (140 c.c.), and sufficient methyl alcohol to produce a homogeneous solution was refluxed for 5 hr.; the product, isolated with ether, crystallised from benzene–light petroleum (b. p. 60—80°) in needles (11·5 g.), m. p. 155—156° (Fritzsch, *loc. cit.*, gives m. p. 155—156°).

5 : 6 : 7-*Trihydroxy*-4-*methyl*iso*coumarin* (VIII; R = H).—Gallacetol (2 g.) was kept in 80% sulphuric acid (40 c.c.) at 0° for 20 hr The mixture was decomposed with ice, and the precipitate was collected, washed with water, and crystallised from acetone; the *trihydroxymethyl*iso*coumarin* (VIII; R = H) separated in rhombic prisms which effloresced in air forming a powder, melting indefinitely between 260° and 280° (Found : C, 57·6; H, 4·2. $C_{10}H_8O_5$ requires C, 57·7; H, 3·9%).

The trihydroxy-derivative (1·1 g.) in methyl alcohol (25 c.c.) was allowed to react with ethereal diazomethane (from 20 g. of nitrosomethylurea). After 3 days, removal of solvent yielded the trimethyl ether (VIII; R = Me) which crystallised from methyl alcohol in needles (1·2 g.), m. p. 93—94°, identical with the compound obtained from flavellagic acid.

Acetonyl 3 : 4 : 5-*Trimethoxybenzoate*.—3 : 4 : 5-Trimethoxybenzoic acid (10·5 g.), potassium carbonate (3·4 g.), chloroacetone (4·6 c.c.), water (70 c.c.), and sufficient methyl alcohol to produce a clear solution were refluxed for 4 hr. The product, isolated with ether, crystallised from aqueous methyl alcohol in plates (7·2 g.), m. p. 83—84° (Found : C, 58·3; H, 6·3. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%). This *ester* was recovered unchanged after treatment with 80% sulphuric acid (12 vol.) at 0° for 7 days.

Chloromethyl Propyl Ketone.—Butyryl chloride (5 g.) was added to ice-cold ethereal diazomethane (from 40 g. of nitrosomethylurea). After 6 hr. at room temperature, concentrated hydrochloric acid (100 c.c.) was added with stirring, and after a further ½ hr. the ether layer was separated, washed with water, dried, and evaporated. The residue was a colourless lachrymatory oil (4·8 g.), b. p. 153—155°/753 mm. (Levene and Haller, *J. Biol. Chem.*, 1928, **77**, 560,

give 154·5—156°). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in yellow needles, m. p. 138—139° (Found : N, 18·7. $C_{11}H_{13}O_4N_4Cl$ requires N, 18·6%).

2-*Oxopentyl* 3 : 4 : 5-*Trihydroxybenzoate*.—A mixture of gallic acid (2·5 g.), chloromethyl propyl ketone (2·2 g.), potassium carbonate (0·9 g.), water (30 c.c.), and sufficient methyl alcohol to produce a homogeneous solution was refluxed for 4 hr. The *ester*, isolated with ether, separated from toluene as a microcrystalline powder (2·1 g.), m. p. 141—142° (Found : C, 56·5; H, 5·3. $C_{12}H_{14}O_8$ requires C, 56·7; H, 5·5%). It was recovered after treatment with 80% sulphuric acid at 0° for 7 days, and after 4 hours' refluxing in benzene with phosphoric oxide.

Ethyl 5 : 6 : 7-*Trimethoxy*iso*coumarin*-4-*carboxylate* (XII; R = Et).—A mixture of ethyl formate (21 c.c.) and ethyl 6-ethoxycarbonyl-2 : 3 : 4-trimethoxyphenylacetate (XI) (28 g.) was added to potassium ethoxide [prepared from potassium (4·9 g.) and ethyl alcohol (7·2 c.c.)]. After 1 day, water was added and acidification of the red aqueous layer gave an oily formyl derivative which was isolated with ether and cyclised by 20 minutes' heating on a water-bath with concentrated hydrochloric acid (1 c.c.). *Ethyl* 5 : 6 : 7-*trimethoxy*iso*coumarin*-4-*carboxylate*, isolated with ether, crystallised from ethyl alcohol in needles (5 g.), m. p. 105—106° (Found : C, 58·5; H, 5·4. $C_{15}H_{16}O_7$ requires C, 58·4; H, 5·2%).

3 : 4-*Dihydro*-5 : 6 : 7-*trimethoxy*iso*coumarin*-4-*carboxylic Acid* (XIII).—The ethyl ester (XIII; R = Et) (0·77 g.) in acetic acid (50 c.c.) was shaken with 25% palladium–charcoal (0·08 g.) in hydrogen at 50°. After 10 days, removal of the catalyst and the solvent gave a yellow oil (A), which was hydrolysed by 4 hours' boiling with acetic acid (5 c.c.), concentrated hydrochloric acid (2 c.c.), and water (6 c.c.). Dilution with water (40 c.c.) and continuous ether-extraction for 18 hr. yielded a brown oily *acid* which slowly solidified and crystallised from 50% aqueous acetic acid in colourless prisms (0·4 g.), m. p. 160—161° (decomp.) (Found : C, 55·1; H, 5·2. $C_{13}H_{14}O_7$ requires C, 55·3; H, 5·0%).

Methyl β-*Hydroxy*-α-(2 : 3 : 4-*trimethoxy*-6-*methoxycarbonylphenyl*)*propionate*.—(*a*) 3 : 4-Dihydro-5 : 6 : 7-trimethoxy*iso*coumarin-4-carboxylic acid was dissolved in hot water. On cooling, an oil separated and slowly solidified; this was taken up in ether, dried, and mixed with excess of ethereal diazomethane. (*b*) The yellow oil produced as in the preceding paragraph was hydrolysed with hot 6% potassium hydroxide solution. Acidification and extraction with ether gave a white solid, which was allowed to react with excess of ethereal diazomethane for 2 hr. In both cases removal of the ether gave *methyl* β-*hydroxy*-α-(2 : 3 : 4-*trimethoxy*-6-*methoxycarbonylphenyl*)*propionate*, prisms (methyl alcohol), m. p. 110° (decomp.) (Found : C, 54·6; H, 5·8. $C_{15}H_{20}O_8$ requires C, 54·9; H, 6·1%).

7-*Cyanomethyl*-4 : 5 : 6-*trimethoxyphthalide* (XVI; R = CN).—A solution of 7-chloromethyl-4 : 5 : 6-trimethoxyphthalide (XVI; R = Cl) (4·7 g.; Haworth, Moore, and Pauson, *loc. cit.*) in alcohol (30 c.c.) was added to a solution of sodium cyanide (1·7 g.) in water (10 c.c.). After boiling for 3 hr., the mixture was cooled, then poured into an equal volume of dilute hydrochloric acid, and the brown solid was collected; crystallisation from methyl alcohol gave 7-*cyanomethyl*-4 : 5 : 6-*trimethoxyphthalide* as colourless prisms (3·6 g.), m. p. 105—106° (Found : C, 59·2; H, 4·9; N, 5·2. $C_{13}H_{13}O_5N$ requires C, 59·3; H, 4·9; N, 5·3%). The nitrile was soluble in warm dilute sodium hydroxide, and was recovered by acidification.

7-*Carboxymethyl*-4 : 5 : 6-*trimethoxyphthalide*.—The nitrile (XVI; R = CN) (1 g.) was refluxed with 20% aqueous potassium hydroxide (10 c.c.) until evolution of ammonia ceased. Acidification then yielded the *acid* (XVI; R = CO_2H) which crystallised from hot water in prisms (0·9 g.), m. p. 124—125° [Found : equiv. (cold), 281; (hot), 142·5; C, 55·2; H, 4·9%. $C_{13}H_{14}O_7$ requires equiv. (cold), 282; (hot), 141; C, 55·3; H, 5·0%].

7-*Hydroxymethyl*-4 : 5 : 6-*trimethoxyphthalide* (XVI; R = OH).—The chloromethylphthalide (XVI; R = Cl) (1·5 g.) was boiled with 5% aqueous sodium hydroxide (50 c.c.) for 3 hr. Acidification and extraction with ether gave the *hydroxymethylphthalide* which crystallised from benzene–light petroleum (b. p. 60—80°) in needles (0·8 g.), m. p. 87—88° (Found : C, 56·9; H, 5·9. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·6%), depressed to 78—80° on admixture with the starting material and giving a positive Zerewitinoff test.

Chloromethylation of 4 : 5 : 6-*Trimethoxyphthalide*.—5 : 4 : 6-Trimethoxyphthalide (1 g.), 40% aqueous formaldehyde (0·7 c.c.), and concentrated hydrochloric acid (4 c.c.) were warmed on a steam-bath for 1 hr. The product crystallised from light petroleum (b. p. 60—80°) in needles (0·3 g.), m. p. 83—84°, undepressed on admixture with the product obtained by Haworth, Moore, and Pauson (*loc. cit.*) by chloromethylation of methyl 3 : 4 : 5-trimethoxybenzoate.

3-*Diazoacetyl*-4 : 5 : 6-*trimethoxyphthalide* (XIV; R = CHN_2).—4 : 5 : 6-Trimethoxyphthalide-3-carboxylic acid (Bargellini and Molina, *loc. cit.*) (1 g.) was refluxed for 1 hr. with excess of thionyl chloride. Evaporation then yielded the oily chloride (XIV; R = Cl) which

with ethereal diazomethane (from 2·5 g. of nitrosomethylurea) during 10 hr. gave the *diazo*-ketone, pale yellow needles (0·3 g.) (from methyl alcohol), m. p. 104—105° (decomp.) (Found: C, 53·5; H, 4·2; N, 9·6. $C_{13}H_{12}O_6N_2$ requires C, 53·4; H, 4·1; N, 9·6%).

3-Acetyl-4 : 5 : 6-trimethoxyphthalide (XIV; R = Me).—The diazo-ketone (XIV; R = CHN_2) (0·5 g.) was treated in chloroform (30 c.c.) at 50° with 50% hydriodic acid (10 c.c.). When nitrogen evolution had ceased, the chloroform layer was washed with water and sodium thiosulphate solution, and dried. Removal of the solvent gave a brown solid, which crystallised from methyl alcohol (charcoal) in colourless needles (0·2 g.), m. p. 75—76°, undepressed on admixture with 3-acetyl-4 : 5 : 6-trimethoxyphthalide prepared from galloflavin (Haworth and McLachlan, *loc. cit.*).

The following experiments were carried out by Dr. P. R. Jefferies.

Diethyl 5 : 6 : 7-Trimethoxyisocoumarin-3 : 4-dicarboxylate (XVII; R = R′ = Et).—A mixture of diethyl oxalate (2·0 g.) and ethyl 6-ethoxycarbonyl-2 : 3 : 4-trimethoxyphenylacetate (XI) (3·0 g.) was added to potassium ethoxide (from 0·8 g. of potassium) in ether (50 c.c.). After 1 day at room temperature, water was added, the red aqueous layer was acidified, and the product, isolated with ether as a brown oil, was cyclised by 3 hours' heating at 140°. The dicarboxylic ester (XVII; R = R′ = Et) crystallised from ethyl alcohol in needles (1·9 g.), m. p. 159—162° (Found: C, 56·7; H, 5·7. $C_{18}H_{20}O_9$ requires C, 56·9; H, 5·3%).

5 : 6 : 7-Trimethoxyisocoumarin-3-carboxylic Acid (X; R = H).—The ester (XVII; R = R′ = Et) (0·5 g.) was refluxed with dilute sulphuric acid (20 c.c.) and acetic acid (5 c.c.) for 2 days. The product (X; R = H) separated on cooling and crystallised from ethyl alcohol in slender needles (0·35 g.), m. p. 262—264° (Found: C, 55·9; H, 4·6. Calc. for $C_{13}H_{12}O_7$: C, 55·7; H, 4·3%), undepressed on admixture with a specimen prepared by pyrolysis of trimethylchebulic acid as described in the preceding paper (p. 3616). Tschitschibabin *et al.*, *loc. cit.* give m. p. 254°.

When this hydrolysis was interrupted after 10 hr., some acid (X; R = H) was obtained but dilution of the alcoholic mother-liquors with water gave an *acid ester*, probably (XVIII; R = H; R′ = Et), which crystallised from 50% aqueous alcohol in prisms, m. p. 174—175° (Found: C, 54·2; H, 4·8. $C_{16}H_{18}O_9$ requires C, 54·2; H, 5·0%).

Methyl 5 : 6 : 7-Trimethoxyisocoumarin-3-carboxylate (X; R = Me).—This ester, prepared with ethereal diazomethane, separated from methyl alcohol in needles, m. p. 154—155° (Found: C, 57·4; H, 4·9. Calc. for $C_{14}H_{14}O_7$: C, 57·1; H, 6·8%) undepressed on admixture with the specimen described in the preceding paper (p. 3616). The acid chloride, prepared by use of refluxing thionyl chloride (5 parts) for 3 hr., separated from benzene in long prisms, m. p. 163—164° (Found: C, 52·6; H, 3·7. Calc. for $C_{13}H_{11}O_6Cl$: C, 52·3; H, 3·7%), identical with the chloride described in the preceding paper (p. 3616). The ethyl ester, prepared from the acid chloride and alcohol, crystallised from alcohol in needles, m. p. 118° (Found: C, 58·5; H, 5·5. Calc. for $C_{15}H_{16}O_7$: C, 58·4; H, 5·2%), undepressed on admixture with the specimen prepared in the preceding paper (p. 3616).

3-Diazoacetyl-5 : 6 : 7-trimethoxyisocoumarin.—The acid chloride, m. p. 163—164° (0·9 g.), described above, was added in small portions to ethereal diazomethane (from 3 g. of nitrosomethylurea), and after 15 hr. the yellow precipitate was collected and crystallised from benzene; *3-diazoacetyl-5 : 6 : 7-trimethoxyisocoumarin* was obtained as pale yellow needles (0·55 g.), m. p. 158—159° (decomp.) (Found: N, 8·9. $C_{14}H_{12}O_6N_2$ requires N, 9·2%).

Methyl 5 : 6 : 7-Trimethoxy-3-isocoumarinylacetate.—The diazoketone (0·4 g.) in methyl alcohol (15 c.c.) was heated at 50° and dry silver oxide (0·1 g.) added; a further quantity of silver oxide (0·15 g.) was added in five portions at intervals of 10 min. The mixture was refluxed for 2 hr., filtered, and evaporated, and the resulting yellow oil was chromatographed in benzene (5 c.c.) on alumina (10 g.). Elution with the same solvent gave a solid fraction which yielded *methyl 5 : 6 : 7-trimethoxy-3-isocoumarinylacetate* as colourless prisms (0·06 g.), m. p. 127—128° (Found: C, 58·7; H, 5·2. $C_{15}H_{16}O_7$ requires C, 58·4; H, 5·2%) after crystallisation from benzene–light petroleum (b. p. 60—80°).

3 : 4-Dihydro-5 : 6 : 7-trimethoxyisocoumarin-3-carboxylic Acid.—Ethyl 5 : 6 : 7-trimethoxy-*iso*coumarin-3-carboxylate (X; R = Et) (4·4 g.) in acetic acid (125 c.c.) was reduced in presence of 25% palladium–charcoal (0·5 g.) at 50°. After 2 days the catalyst and solvent were removed and the 3 : 4-dihydro-ester was distilled at 250° (bath)/0·1 mm. It crystallised from alcohol as prisms (3·7 g.), m. p. 84—85° (Found: C, 57·8; H, 5·7. Calc. for $C_{15}H_{18}O_7$: C, 58·1; H, 5·8%), undepressed on admixture with a specimen obtained as described in the preceding paper (p. 3616). Hydrolysis for 2 hr. with boiling hydrochloric acid (10 vol.) and water (30 vol.) gave the *acid*, which crystallised from hot water in needles, m. p. 166—167° (Found: C, 55·2; H, 5·1. $C_{13}H_{14}O_7$ requires C, 55·3; H, 5·0%).

Our thanks are offered to the Department of Scientific and Industrial Research for a maintenance grant to H. K. P., to the University of Western Australia for a Hackett Research Studentship to P. R. J., and to the Imperial Chemical Industries Limited for a grant which has defrayed some of the expenses of this research.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, June 12th*, 1954.]

Structure and Reactivity of Anhydro-sugars. Part III. An Interpretation of Some Reactions of* 3 : 6-*Anhydro*-D-*hexoses.*

By A. B. FOSTER, W. G. OVEREND, and G. VAUGHAN.

[Reprint Order No. 5037.]

Syntheses of phenyl 3 : 6-anhydro-α-D-galactopyranoside, and of phenyl 3 : 6-anhydro-α-D-glucopyranoside and derivatives thereof, are described. The action of acids on these anhydro-compounds has been investigated. An explanation is put forward, on the basis of conformational analysis, of the anomerisations produced by methanolic hydrogen chloride on the derivatives of 3 : 6-anhydro-D-glucose, 3 : 6-anhydro-D-galactose, 3 : 6-anhydro-D-mannose, and their 2-deoxy-analogues, as described in the preceding paper.

THE dicyclic systems in the methyl 3 : 6-anhydro-D-glucosides and methyl 3 : 6-anhydro-D-galactosides and their derivatives are affected in unusual ways by acidic reagents (for a full account see Haworth, Jackson, and Smith, *J.*, 1940, 620; Haworth, Owen, and Smith, *J.*, 1941, 88; for a review see Peat, *Adv. Carbohydrate Chem.*, 1946, **2**, 37). In the preceding paper we described an extension of this work of Haworth *et al.* (*loc. cit.*) and outlined the preparation and some reactions with acidic reagents of derivatives of 3 : 6-anhydro-D-mannose, 3 : 6-anhydro-2-deoxy-D-glucose, and 3 : 6-anhydro-2-deoxy-D-galactose.

From an examination of models, Haworth, Owen, and Smith (*loc. cit.*) concluded that the disposition of the 4- and 5-hydroxyl groups in the methyl 3 : 6-anhydro-D-glucosides allows the formation of two distinct dicyclic systems: the hydrofuran 3 : 6-anhydro-ring can be formed with the sugar in either the pyranose or the furanose form. There is considerable strain when the sugar is in the pyranose form, but little when it is in the furanose form. Hence the pyranose ⟶ furanose (P ⟶ F) conversion observed on treating methyl 3 : 6-anhydro-α(or β)-D-glucopyranoside with methanolic hydrogen chloride is an intramolecular rearrangement with loss of strain. In the galactose series a P ⟶ F rearrangement is impossible for steric reasons (see Haworth, Owen, and Smith, *loc. cit.*) and so the pyranose derivatives are converted into the strainless open-chain form.

The above workers demonstrated that the transformations (P ⟶ F, and α ⟶ β) observed with the methyl 3 : 6-anhydro-D-glycosides did not pass through a stage involving the free reducing sugar. Peat (*loc. cit.*) suggested that the rearrangements proceed by proton attack on the oxygen atom in the pyran ring with the intermediate formation of an ion in which $C_{(1)}$ of the sugar is a carbonium cation. The nature of substituents on $C_{(1)}$ will affect the ease with which it can be converted into a carbonium cation. Consequently in a consideration of the rearrangements occurring with methyl 3 : 6-anhydro-D-hexosides it was thought worth while to examine the behaviour of phenyl 3 : 6-anhydro-D-hexosides.

Phenyl α-D-galactopyranoside was converted into phenyl 3 : 6-anhydro-α-D-galactoside by the procedure described in the preceding communication. Methylation readily afforded the 2 : 4-di-*O*-methyl derivative. Similarly, phenyl 3 : 6-anhydro-α-D-glucopyranoside was synthesised, and was found to be unchanged after treatment with acidic reagents (0·1N-sulphuric acid, or methanolic 1% hydrogen chloride) at room temperature. More vigorous conditions (*e.g.*, 0·1N-sulphuric acid at 100°) result in hydrolysis and 3 : 6-anhydro-D-glucose can be isolated. A P ⟶ F rearrangement was not observed in any experiment with

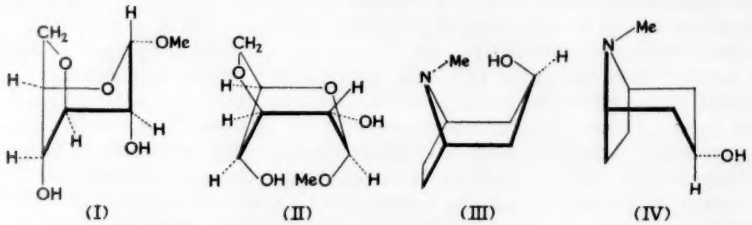
* Part II, *J.*, 1954, 3367.

phenyl 3 : 6-anhydro-α-D-glucopyranoside. Furthermore, no α ⟶ β isomerisation was found when phenyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-α-D-galactoside was treated with hydrogen chloride in non-hydroxylic solvents. These results can be explained satisfactorily on Peat's ionic mechanism. The substitution of the methyl group at $C_{(1)}$ by the more electrophilic phenyl residue would tend to stabilise the bond between $C_{(1)}$ and the oxygen atom in the pyran ring, thereby reducing protonation of the oxygen atom in the ring; the tendency to form the carbonium-cation intermediate would be reduced and so intramolecular rearrangement inhibited. It is very probable that the same ionic mechanism operates during the α ⟶ β anomerisations and so this conversion also would be expected to be sluggish or non-existent for phenyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-α-D-galactoside.

Although the mechanism suggested by Peat (*loc. cit.*) explains the manner of the P ⟶ F and α ⟶ β rearrangements studied by Haworth *et al.* (*loc. cit.*), and the loss of molecular strain by ring contraction clearly causes the former change, reasons for the greater stability of the β- over the α-form have not been outlined. It is our purpose in this communication to propose a possible explanation.

The stereochemistry of pyran derivatives is similar to that of *cyclo*hexane compounds (see Angyal and Mills, *Ann. Rev. Pure Appl. Chem.*, 1952, **2**, 185) and the explanation now put forward is based on the concept of non-bonded interactions which has been developed from considerations of the chemical reactivity of *cyclo*hexane compounds (cf. Barton, *Chem. and Ind.*, 1953, 664; *J.*, 1953, 1027).

When a 3 : 6-anhydro-bridge is introduced into methyl α-D-glucopyranoside, vibration of the molecule at $C_{(3)}$–$C_{(4)}$–$C_{(5)}$ is prevented and so (I) and (II) are the two possible conformations of methyl 3 : 6-anhydro-α-D-glucopyranoside. Both (I) and (II) may be regarded as 6- and 7-membered ring systems in which the chair form of the pyran ring necessitates the 7-membered ring's being in a boat form, and *vice versa*. The possible conformations of methyl 3 : 6-anhydro-D-hexosides therefore bear a close resemblance to the structures which occur in tropine and ψ-tropine. Sparke (*Chem. and Ind.*, 1953, 749) indicates that (IV) probably represents the more stable conformation of ψ-tropine, although the energy barrier between the forms (III) and (IV) is low (see also Cookson, *Chem. and*



(I) (II) (III) (IV)

Ind., 1953, 337). Now, (I) and (II) may also be regarded as composed of 5- and 6-membered rings fused together. The 5-membered hydrofuran ring will tend to exist as nearly planar as possible in both structures (I and II), and the shape of the molecule will therefore depend upon the non-bonded interactions between substituents at $C_{(1)}$ and $C_{(2)}$ with the hydrofuran ring and substituents attached thereto.

The important non-bonded interactions which occur in the methyl 3 : 6-anhydro-D-hexosides, their 2-deoxy-analogues, and the methyl ethers of these compounds can readily be enumerated and assigned estimated values. The values ascribed to the non-bonded interactions (or i-units) are arbitrary figures arrived at from a consideration, with the aid of models, of the geometry of the molecules. The maximum of 10 was assigned to the interaction which introduces most strain into the molecule, *i.e.*, the interaction occurring when methoxyl residues are attached at $C_{(1)}$ and $C_{(4)}$ of the pyran ring when it is in the boat conformation. Values for other interactions can be scaled accordingly, and it follows that the greater the value of the i-unit of a particular arrangement of atoms, the greater is the strain within the molecule, *i.e.*, the higher the i-unit the lower is the molecular stability. The i-units for the α- and the β-forms of the methyl anhydrohexosides studied by Haworth

et al. (*loc. cit.*) and by the authors (preceding paper) are shown in the Table for the boat and chair conformations of the pyran ring.

From a consideration of the strain introduced into the possible conformations by substituents at $C_{(1)}$, $C_{(2)}$, and $C_{(4)}$ in the anhydro-compounds it is now suggested that the stable conformations (*i.e.*, those with the smallest number of i-units) of methyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-D-galactopyranoside and -D-glucopyranoside are those in which the β-isomer possesses the 6-membered pyran (sugar) ring in the boat form.

It is well known that methyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-α-D-glucoside is converted by ethereal or chloroformic hydrogen chloride into the β-isomer. Likewise from the Table it would be expected that the most stable form of methyl 2 : 4-di-*O*-methyl-D-mannoside

3 : 6-Anhydro-derivative (pyranose form)	Isomer	A	B	C	D	E	F
Methyl D-glucoside	α	c	**5**	**9**	c	c or b	bβ
		b	**8**	**10**			
	β	c	**8**	**12**	b	b	
		b	**4**	**5**			
Methyl D-galactoside	α	c	**3**	**5**	c	c or b	bβ
		b	**5**	**5**			
	β	c	**6**	**8**	b	b	
		b	**3**	**3**			
Methyl D-mannoside	α	c	**3**	**5**	c	c	cα
		b	**10**	**13**			
	β	c	**6**	**8**	c or b	c or b	
		b	**6**	**8**			
Methyl 2-deoxy-D-glucoside	α	c	**3**	**5**	c	c	cα or bβ
		b	**8**	**10**			
	β	c	**6**	**8**	b	b	
		b	**4**	**5**			
Methyl 2-deoxy-D-galactoside	α	c	**1**	**1**	c	c	cα or (bβ)
		b	**5**	**5**			
	β	c	**4**	**4**	b	c or b	
		b	**3**	**3**			

A = Conformation (c = chair form, b = boat form).
B = Total i-units.
C = Total i-units in fully methylated derivative.
D = Predicted most stable conformation.
E = Predicted most stable conformation in fully methylated derivative.
F = Predicted most stable form in αβ-mixture of fully methylated derivative.

would be the α-form in the chair conformation. Therefore an acid-catalysed β ⟶ α anomerisation should occur under the conditions which effect the α ⟶ β change in the corresponding derivatives of 3 : 6-anhydro-D-glucose and 3 : 6-anhydro-D-galactose. In the previous paper this β ⟶ α transformation in the mannose series was described. Further, from the Table it would be expected that methyl 3 : 6-anhydro-2-deoxy-4-*O*-methyl-α-D-glucoside and -galactoside under the same acidic conditions would be converted into αβ-mixtures, and this is in accordance with experiment (see previous paper). (It is considered that a difference of about 3 i-units is required for a complete transformation of one anomer into the other when both possible conformations exhibit instability denoted by 5 or more i-units.) The αβ-mixture of methyl 3 : 6-anhydro-2-deoxy-4-*O*-methyl-D-glucoside would be expected to contain about 50% of each anomer since the chair form of the α-isomer and the boat form of the β-isomer appear to be under the same strain. Similar reasoning indicates that the α-anomer would be the major component of the αβ-product of acid treatment of methyl 3 : 6-anhydro-2-deoxy-4-*O*-methyl-α-D-galactoside. Experimental findings are in agreement with these conclusions (see previous paper). Likewise there is good agreement between experiments and deductions based on the values in the Table regarding the relative stabilities and rates of reaction of the methyl 3 : 6-anhydro-D-hexosides studied. It is realised that this treatment involves some over-simplification of the problem since dipole-moment and hydrogen-bonding effects are neglected, but it is our opinion that it provides at least a partial explanation of the α–β-isomerisations observed with this class of compounds.

Experimental

Phenyl 6-O-*Toluene*-p-*sulphonyl*-α-D-*galactoside*.—Phenyl α-D-galactoside (9·95 g.) and toluene-*p*-sulphonyl chloride (7·35 g.) were allowed to react in pyridine (200 ml.) at 0° for 48 hr. and at room temperature for a further 3 hr. After isolation in the usual manner and recrystallisation from ethanol *phenyl* 6-O-*toluene* p-*sulphonyl*-α-D-*galactoside* (8·0 g., 52%) was obtained as colourless plates, m. p. 148°, $[\alpha]_D^{18}$ +90° (*c*, 1·0 in pyridine) (Found: C, 55·1; H, 5·6; S, 7·7. $C_{19}H_{22}O_8S$ requires C, 55·6; H, 5·4; S, 7·8%).

Phenyl 3 : 6-*Anhydro*-α-D-*galactoside*.—Phenyl 6-*O*-toluene-*p*-sulphonyl-α-D-galactoside (4·5 g.) was treated in ethanol (50 ml.) with N-sodium hydroxide (18 ml.) at 80—85° for 2 hr. The solution was neutralised (solid carbon dioxide) and concentrated under diminished pressure to a solid residue which was extracted with dry acetone. Evaporation of the extract gave a product which was recrystallised from chloroform–light petroleum (b. p. 60—80°). *Phenyl* 3 : 6-*anhydro*-α-D-*galactoside* was obtained in almost quantitative yield, having m. p. 152°, $[\alpha]_D^{21}$ +48·2° (*c*, 1·12 in $CHCl_3$) (Found: C, 60·8; H, 5·9. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%).

3 : 6-*Anhydro*-D-*galactose*.—Phenyl 3 : 6-anhydro-α-D-galactoside (0·223 g.) in water (20 ml.) and 2N-sulphuric acid (1 ml.) were heated at 100° and reaction followed polarimetrically. After 120 min. the solution was neutralised ($BaCO_3$) and after filtration was evaporated to dryness. The syrupy residue was extracted with ethanol. By removal of the solvent from the extract, 3 : 6-anhydro-D-galactose (0·1 g., 67%), $[\alpha]_D^{20}$ +20° (*c*, 1·0 in H_2O), was obtained as a colourless glass. The product, heated with phenylhydrazine (0·23 g.) in 36% aqueous acetic acid (5·0 ml.) at 70—75° for 2 hr., gave 3 : 6-anhydro-D-galactose phenylosazone, m. p. 216° (Found: N, 16·6. Calc. for $C_{18}H_{20}O_3N_4$: N, 16·5%). Haworth, Jackson, and Smith (*J.*, 1940, 620) report m. p. 216°.

Phenyl 3 : 6-*Anhydro*-2 : 4-*di*-O-*methyl*-α-D-*galactoside*.—Phenyl 3 : 6-anhydro-α-D-galactoside (1·5 g.) was methylated with methyl iodide and silver oxide in the presence of sufficient dry acetone to effect dissolution of the glycoside. Four treatments were carried out and *phenyl* 3 : 6-*anhydro*-2 : 4-*di*-O-*methyl*-α-D-*galactoside* (1·5 g., 90%) was obtained as a colourless mobile liquid, b. p. 165—170°/0·01 mm., $[\alpha]_D^{20}$ +45·5° (*c*, 1·8 in $CHCl_3$), n^{20} 1·5227 (Found: C, 63·9; H, 6·9. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%).

Acidic Hydrolysis of Phenyl 3 : 6-*Anhydro*-2 : 4-*di*-O-*methyl*-α-D-*galactoside*.—2N-Sulphuric acid (1 ml.) was added to a solution of phenyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-α-D-galactoside (0·316 g.) in methanol (20 ml.), and the solution was heated under reflux, reaction being complete (polarimetry) in 170 min. The mixture was neutralised and worked up in the usual way. 3 : 6-Anhydro-2 : 4-di-*O*-methyl-D-galactose (0·15 g.) was obtained as a colourless glass, $[\alpha]_D^{20}$ +18° (*c*, 2·28 in H_2O), which was converted into crystalline 3 : 6-anhydro-2 : 4-di-*O*-methyl-*N*-phenyl-D-galactosylamine, m. p. 120°, $[\alpha]_D^{20}$ +52° (equil.; *c*, 0·2 in EtOH) {Haworth, Jackson, and Smith, *loc. cit.*, report m. p. 123°, $[\alpha]_D^{20}$ +56° (equil.)}.

Action of Chloroformic and Methanolic Hydrogen Chloride on Phenyl 3 : 6-*Anhydro*-2 : 4-*di*-O-*methyl*-α-D-*galactoside*.—A solution of the galactoside (0·443 g.) in chloroform (5 ml.) was saturated with dry hydrogen chloride and kept at room temperature for 3 days. No change in specific rotation occurred during this period. After neutralisation (Ag_2CO_3), filtration, and evaporation, unchanged galactoside (0·35 g.), b. p. 150—160°/0·01 mm., n^{20} 1·5222, $[\alpha]_D^{19}$ +49·2 (*c*, 1·3 in $CHCl_3$), was recovered. This glycoside was also unaffected by 1% methanolic hydrogen chloride for 24 hr. at room temperature.

Phenyl 3 : 6-*Anhydro*-α-D-*glucoside*.—A solution of phenyl α-D-glucopyranoside (10 g.) in dry pyridine (200 ml.) was cooled to 0°. During 1 hr. toluene-*p*-sulphonyl chloride (7·4 g.) was added and then the mixture was set aside at 0° for 48 hr. and thereafter at room temperature for 3 hr. Syrupy phenyl 6-*O*-toluene-*p*-sulphonyl-α-D-glucoside (5·1 g.) was isolated by the methods previously described. This syrup (5·0 g.) in ethanol (100 ml.) was converted by N-sodium hydroxide (20 ml.) at 80—85° during 2 hr. into *phenyl* 3 : 6-*anhydro*-α-D-*glucoside* which was extracted with ether–acetone (1 : 1, v/v). Distillation of the crude product yielded the anhydroglucoside as a colourless syrup (1·5 g., 16%), b. p. 170—175°/0·01 mm., $[\alpha]_D^{20}$ +21·1° (*c*, 1·3 in H_2O). Trituration with ether induced crystallisation and after recrystallisation from ether the colourless crystals had m. p. 85—86°, $[\alpha]_D^{20}$ +21·2° (*c*, 1·5 in H_2O) (Found: C, 60·2; H, 5·8. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%).

Action of Dilute Sulphuric Acid on Phenyl 3 : 6-*Anhydro*-α-D-*glucopyranoside*.—Phenyl 3 : 6-anhydro-α-D-glucopyranoside (0·19 g.) in 0·1N-sulphuric acid (20 ml.) underwent no reaction during several days ($[\alpha]_D$ +21·1° const.) and unchanged starting material was recovered.

If the compound (0·24 g.) in water (20 ml.) was treated with 2N-sulphuric acid (1·0 ml.) at

100°, reaction was complete (polarimetry) in 30 min. Neutralisation ($BaCO_3$) and evaporation gave a syrup from which **3 : 6**-anhydro-D-glucose (0·15 g., 89%), m. p. and mixed m. p. 121°, $[\alpha]_D^{20}$ +54° (*c*, 2·1 in H_2O), was isolated by extraction with ethanol.

Action of Methanolic Hydrogen Chloride on Phenyl **3 : 6**-*Anhydro*-α-D-*glucopyranoside*.—The substance was recovered unchanged after treatment with 1% methanolic hydrogen chloride at room temperature for 24 hr.

Thanks are expressed to Professor M. Stacey, F.R.S., for his close interest. One of us (G. V.) thanks the Dunlop Rubber Co. for a maintenance grant. Part of the expenses of this work were covered by a grant from Messrs. Tootal, Broadhurst and Lee Co.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

[*Received, February 3rd*, 1954.]

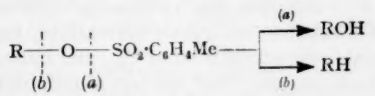
Deoxy-sugars. Part XXVI. The Cleavage of Sulphonic Esters with Lithium Aluminium Hydride.*

By R. ALLERTON and W. G. OVEREND.

[Reprint Order No. 5247.]

Cleavage with lithium aluminium hydride of the 2-toluene-*p*-sulphonates and 2-methanesulphonates of methyl β-L-arabinoside and its **3 : 4**-*O*-*iso*propylidene derivative has been studied. Both esters of the latter sugar undergo direct cleavage and methyl **3 : 4**-*O*-*iso*propylidene-β-L-arabinoside is regenerated. Methyl 2-*O*-methanesulphonyl(or 2-*O*-toluene-*p*-sulphonyl)-β-L-arabinoside gave methyl β-L-arabinoside, **2 : 3**-anhydro-β-L-riboside, 2-deoxy-β-L-riboside, and 3-deoxy-β-L-xyloside (-riboside). These results are compared with those obtained by the hydrogenolysis of sulphonic esters of sugars with sodium amalgam (Vargha, Puskás, and Nagy, *J. Amer. Chem. Soc.*, 1948, **70**, 261) and with Raney nickel and hydrogen (Kenner and Murray, *J.*, 1949, S 178).

THE reduction of toluene-*p*-sulphonic esters has been studied by Schmid and Karrer (*Helv. Chim. Acta*, 1949, **32**, 1371) (cf. also Vis and Karrer, *ibid.*, 1954, **37**, 378), using lithium aluminium hydride, and by Kenner and Murray (*J.*, 1949, S 178) using Raney nickel and hydrogen. The Swiss authors concluded that there are two distinct reactions with lithium aluminium hydride, namely, hydrogenolysis (*a*) with preservation of the hydroxyl group and (*b*) with fission of the hydroxyl group, as depicted :



From the examples studied it appeared that although aryl toluene-*p*-sulphonates react according to scheme (*a*), alkyl toluene-*p*-sulphonates (including esters of carbohydrates) react according to either scheme. Kenner and Murray (*loc. cit.*; see also *J.*, 1950, 406), however, reported that hydrogenation in the presence of Raney nickel converts aryl toluene-*p*-sulphonates into aromatic hydrocarbons and the alkyl esters into alcohols; in agreement with Trevoy and Brown (*J. Amer. Chem. Soc.*, 1949, **71**, 1675), they regard lithium aluminium hydride as a source of potential hydride ions and ascribe to steric hindrance the exceptional reductions noted in the sugar series with this reagent. In this paper we report the action of lithium aluminium hydride on other toluene-*p*-sulphonates and methanesulphonates of some L-arabinose derivatives.

By heating under reflux a suspension of methyl **3 : 4**-*O*-*iso*propylidene-2-*O*-toluene-*p*-sulphonyl-β-L-arabinoside in dry ether with lithium aluminium hydride, a syrup (A) was

* Part XXV, *J.*, 1954, 3367.

formed, which on mild acidic hydrolysis yielded only methyl β-L-arabinoside and on complete hydrolysis only arabinose. From these and other tests it became apparent that the syrup was methyl 3 : 4-*O*-*iso*propylidene-β-L-arabinoside (see Honeyman, *J.*, 1946, 990; Overend and Stacey, *J.*, 1949, 1235). Methyl 3 : 4-*O*-*iso*propylidene-2-*O*-methanesulphonyl-β-L-arabinoside gave a similar result. Clearly both compounds reacted with lithium aluminium hydride according to scheme "*a*."

Hydrogenolysis of methyl 2-*O*-toluene-*p*-sulphonyl-β-L-arabinoside with lithium aluminium hydride also yielded a syrup, but in this case chromatography of a hydrochloric acid hydrolysate revealed the presence of L-arabinose, 2-deoxy-L-ribose, 3-deoxy-L-xylose (-ribose), and 3-chloro-3-deoxy-L-xylose. In another experiment on a larger scale methyl β-L-arabinoside, methyl 2 : 3-anhydro-β-L-riboside, and methyl 2-deoxy-β-L-riboside were isolated, and chromatography of the syrupy residue revealed that it contained some methyl 3-deoxy-β-L-xyloside (-riboside). It is interesting in this connection that Vargha, Puskás, and Nagy (*J. Amer. Chem. Soc.*, 1948, **70**, 261) report that in sodium amalgam reduction of toluene-*p*-sulphonic esters of compounds containing some free hydroxyl groups competitive reactions occur: in addition to reduction products, anhydro-bodies may be formed by the loss of toluene-*p*-sulphonic acid. Kenner and Murray (*loc. cit.*) found that such esters (*e.g.*, methyl 2-toluene-*p*-sulphonyl-α-L-arabinoside) were readily converted by Raney nickel and hydrogen into sulphur-free materials, but that only small quantities of the expected products could be separated in the pure state, probably owing to the formation of anhydro-sugars. The treatment of the syrupy product with hydrochloric acid before the chromatographic examination results not only in hydrolysis of the glycoside group, but also in rupture of the anhydro-ring in methyl 2 : 3-anhydro-β-L-riboside, with the formation predominantly of 3-chloro-3-deoxy-L-xylose (Allerton and Overend, *J.*, 1951, 1480). Similarly it is probable that at least part of the methyl 2-deoxy-β-L-riboside arises from the action of excess of lithium aluminium hydride on the methyl 2 : 3-anhydro-β-L-riboside previously formed, it being well known that 2 : 3-anhydro-sugars are cleaved by lithium aluminium hydride with the formation of deoxy-sugars (Prins, *J. Amer. Chem. Soc.*, 1948, **70**, 3955) and, in particular, that methyl 2 : 3-anhydro-β-D-riboside gives methyl 2-deoxy-β-D-riboside and methyl 3-deoxy-β-D-xyloside (-riboside) (Allerton and Overend, *loc. cit.*). Although in the experiments described above, methyl 3-deoxy-β-L-xyloside was not isolated in crystalline form, its undoubted presence in the syrupy reaction mixture was demonstrated by chromatography. It is difficult to conceive how this 3-deoxy-sugar could arise except by the action of lithium aluminium hydride on methyl 2 : 3-anhydro-β-L-riboside, which would yield also methyl 2-deoxy-β-L-riboside.

However some of the methyl 2-deoxy-β-L-riboside is probably formed by direct reduction of methyl 2-*O*-toluene-*p*-sulphonyl-β-L-arabinoside according to a reaction of type (*b*) as noted by Schmid and Karrer (*loc. cit.*). From previous investigations it is apparent that treatment of methyl 2 : 3-anhydro-D(or L)-riboside with nucleophilic reagents leads mainly to the formation of 3-substituted xylose derivatives, together with much smaller amounts of derivatives of arabinose substituted at $C_{(2)}$, and indeed we have already demonstrated (Allerton and Overend, *loc. cit.*) that lithium aluminium hydride converts methyl 2 : 3-anhydro-β-D-riboside mainly into methyl 3-deoxy-β-D-xyloside. In the present experiments, however, methyl 2-deoxy-β-L-riboside was formed in much larger amount than was the 3-deoxy-analogue, indicating that at least part of the former probably arises by some reaction other than that of excess of lithium aluminium hydride on the 2 : 3-anhydro-pentoside. Furthermore the action of the hydride on methyl 3 : 4-di-*O*-acetyl-2-*O*-toluene-*p*-sulphonyl-β-L-arabinoside gives only methyl β-L-arabinoside and methyl 2-deoxy-β-L-riboside. Since in these experiments cleavage of the acetyl groups also occurred (this was also shown in a separate experiment by treating methyl 2 : 3 : 4-tri-*O*-acetyl-β-L-arabinoside with lithium aluminium hydride: the product was methyl β-L-arabinoside; cf. Jones, Henbest, and Lovell, B.P. Appl. 8549/51 and 8550/51, for reductive cleavage of benzoates), the possibility of anhydro-ring formation must be considered. However, neither methyl 2 : 3-anhydro-β-L-riboside nor methyl 3-deoxy-β-L-xyloside was isolated or even detected chromatographically, which strongly suggests that direct reductive cleavage of the toluene-*p*-sulphonyloxy-group had occurred.

Essentially similar results have been obtained with the corresponding 2-*O*-methanesulphonyl derivatives of L-arabinose, except that relatively greater amounts of methyl β-L-arabinoside and smaller amounts of methyl 2-deoxy-β-L-riboside were formed generally (*i.e.*, reaction " *a* " was even more predominant).

Although the experiments now described lead to a derivative of 2-deoxyribose, they are not useful for its preparation, owing to difficulties encountered in separating the syrupy reaction mixture and the low yield.

Experimental

Treatment of Methyl 2-O-*Toluene*-p-*sulphonyl*-β-L-*arabinoside with Lithium Aluminium Hydride.*—(a) *Initial experiment.* Reduction of methyl 2-*O*-toluene-*p*-sulphonyl-β-L-arabinoside (1 g.) with lithium aluminium hydride (2 g.) was followed by hydrolysis and chromatography, which showed the presence of arabinose, 2-deoxyribose, 3-deoxyxylose, and 3-chloro-3-deoxyxylose.

(b) *Larger-scale experiment.* Lithium aluminium hydride (10 g., 17·5 mols.) was suspended in dry ether (300 c.c.), and methyl 2-*O*-toluene-*p*-sulphonyl-β-L-arabinoside (19 g.) was added during 3 hr., the final 5 g. in solution in dry ether (400 c.c.). After 24 hours' heating under reflux, additional lithium aluminium hydride (5 g.) and dry ether (150 c.c.) were added, and heating was continued for 48 hr. Excess of hydride was eliminated by cautious addition of water. The mixture was filtered and the residue washed thoroughly with water. The combined filtrate and washings were accurately neutralised with 2N-sulphuric acid. A precipitate which formed was removed and the filtrate concentrated to dryness. The white solid residue was extracted with hot ethyl acetate. The small amount of syrupy residue was dissolved in water, and the solution filtered and then concentrated. The syrupy residue (0·864 g.) was separated by ethanol fractionation into an unidentified syrup and methyl β-L-arabinoside (m. p. 169—170°, $[\alpha]_D$ +244·5° in H_2O). On cooling of the ethyl acetate extract a further amount of methyl β-L-arabinoside was deposited (total yield 1·1 g.). Evaporation of the ethyl acetate extract, after separation of the glycoside, afforded a yellow syrup (1·28 g.). A portion (0·173 g.) of this was heated at 100° in 0·05N-hydrochloric acid (3 c.c.) for 40 min. and, after neutralisation (Ag_2O), chromatography in the usual manner showed the presence of methyl β-L-arabinoside, 2 : 3-anhydro-β-L-riboside, 2-deoxy-β-L-riboside, and 3-deoxy-β-L-xyloside. The remainder of the syrup was fractionally distilled and afforded the following fractions: (i) a syrup (0·2936 g.), b. p. 85—95° (bath-temp.)/0·03 mm., which crystallised on nucleation with methyl 2 : 3-anhydro-β-L-riboside, and after recrystallisation from ether had m. p. 46—48°, $[\alpha]_D^{18}$ +52·3° (*c*, 1·26 in $CHCl_3$) {Allerton *et al.*, *J.*, 1951, 1480, report, m. p. 52—53°, $[\alpha]_D^{18}$ −49·2° (*c.*, 1·38 in $CHCl_3$) for the D-isomer}; (ii) a syrup (0·117 g.), b. p. 100—110° (bath-temp.)/0·02 mm., from which a small amount of anhydro-compound was isolated (the remainder did not crystallise); and (iii) a syrup (0·19 g.), b. p. 110—140° (bath-temp.)/0·03—0·04 mm., which crystallised and after recrystallisation from ether was identical with methyl 2-deoxy-β-L-riboside, m. p. 81—83°, $[\alpha]_D^{20}$ +181·8° (*c*, 0·55 in $CHCl_3$) (Deriaz *et al.*, *J.*, 1949, 2836, give m. p. 83—84°, $[\alpha]_D^{20}$ +193°).

Methyl 2-O-*Methanesulphonyl*-β-L-*arabinoside.*—Methyl 3 : 4-*O*-*iso*propylidene-2-*O*-methanesulphonyl-β-L-arabinoside (0·9 g.) (cf. Jones, Kent, and Stacey, *J.*, 1947, 1341) was heated at 100° in N-acetic acid (10 c.c.) for 3 hr. Concentration at 45° then gave a syrup which crystallised. Recrystallisation from ethanol yielded *methyl* 2-O-*methanesulphonyl*-β-L-*arabinoside* (0·75 g., 97%), m. p. 86°, $[\alpha]_D^{15}$ +163° (*c.*, 0·97 in $CHCl_3$) (Found: C, 34·7; H, 6·0. $C_7H_{14}O_7S$ requires C, 34·7; H, 5·8%).

Reduction of Methyl 2-O-*Methanesulphonyl*-β-L-*arabinoside.*—The mixture resulting from the action of lithium aluminium hydride on methyl 2-*O*-methanesulphonyl-β-L-arabinoside was hydrolysed (0·05N-hydrochloric acid). Chromatography then revealed arabinose, 2-chloro-2-deoxyarabinose, 3-chloro-3-deoxyxylose, 2-deoxyribose, and 3-deoxyxylose (mean R_F values respectively were 0·216, 0·250, 0·571, 0·417, and 0·472).

Then methyl 2-*O*-methanesulphonyl-β-L-arabinoside (8·9 g.) was added during 3 hr. to a suspension of powdered lithium aluminium hydride (5 g.) in dry ether (500 c.c.). The mixture was heated under reflux for 3 days and then worked up as described above. Some methyl β-L-arabinoside (m. p. 169—170°) was isolated and concentration of the ethyl acetate extract afforded a syrup (3·61 g.) which crystallised at 0°. This material did not reduce Fehling's solution and gave a positive Dische diphenylamine test. A portion was separated by fractional

distillation in a high vacuum into (i) methyl 2 · 3-anhydro-β-L-riboside, which was obtained as a colourless syrup [b. p. 85—95° (bath-temp.)/0·01 mm.], m. p. 48—50° (after recrystallisation once from ether), $[\alpha]_D^{21}$ +51·6° (*c*, 0·97 in $CHCl_3$) (Found: C, 49·9; H, 6·95. Calc. for $C_6H_{10}O_4$: C, 49·3; H, 6·85%), and (ii) methyl 2-deoxy-β-L-riboside, m. p. 81—83°.

Reduction of Methyl 3 : 4-O-iso*propylidene*-2-O-*methanesulphonyl*-β-L-*arabinoside*.—Powdered lithium aluminium hydride (2 g.) was suspended in dry ether (150 c.c.) in a Soxhlet apparatus. Methyl 3 : 4-*O*-*iso*propylidene-2-*O*-methanesulphonyl-β-L-arabinoside (1 g.) was placed in a thimble in the extractor and the solution refluxed for 4 hr. The mixture was worked up in the usual manner and a sticky solid (A) (0·478 g.) was obtained from which, on mild acidic hydrolysis followed by trituration, only methyl β-L-arabinoside (m. p. 169—170°) was isolated. When the material (A) (0·126 g.) was heated at 100° for 1 hr. in 0·05N-hydrochloric acid no hydrolysis of the glycosidic residue occurred. In N-acid during 7 hr. hydrolysis occurred, as revealed by the onset of reducing power towards Fehling's solution. Chromatography of the hydrolysate after neutralisation with silver oxide revealed arabinose only; no 2-deoxy-L-ribose was detectable.

Repetition of the experiment but with methyl 3 : 4-*O*-*iso*propylidene-2-*O*-toluene-*p*-sulphonyl β-L-arabinoside (1 g.) gave only methyl β-L-arabinoside (0·2 g.).

Reduction of Methyl 3 : 4-*Di*-O-*acetyl*-2-O-*toluene*-p-*sulphonyl*-β-L-*arabinoside*.—Powdered methyl 3 : 4-di-*O*-acetyl-2-*O*-toluene-*p*-sulphonyl-β-L-arabinoside (2 g.) was added to an ice-cold suspension of powdered lithium aluminium hydride (3·82 g.) in dry ether (130 c.c.). The mixture was heated under reflux for 24 hr. and then the excess of hydride was destroyed by water. The suspension was filtered through Filter-cel, and the residue was washed thoroughly with ether and water. The ethereal layer in the combined filtrate and washings was separated and the aqueous phase was re-extracted with ether. After being washed successively with 2N-sulphuric acid, sodium hydrogen carbonate solution, and water, and dried, the ethereal extracts were evaporated to dryness. A negligible residue was obtained. The aqueous layer was neutralised with dilute sulphuric acid and filtered, and the filtrate was evaporated to dryness. The white solid residue was extracted continuously with ethyl acetate for 16 hr. On cooling and nucleation of the extract, crystalline methyl β-L-arabinoside separated and was collected {0·34 g.; m. p. 169—171°, $[\alpha]_D^{20}$ +242·8° (*c*, 1·32 in H_2O)}. The ethyl acetate filtrate therefrom was concentrated to dryness, furnishing a syrup (0·184 g.) which gave a positive Dische test. The syrup was hydrolysed at 100° for 40 min. with 0·05N-hydrochloric acid (3 c.c.), and, after neutralisation, the hydrolysate was examined chromatographically in the usual manner. This showed the presence of arabinose and 2-deoxy-L-ribose only.

When methyl 3 : 4-di-*O*-acetyl-2-*O*-methanesulphonyl-β-L-arabinoside (0·96 g.) was treated similarly, methyl β-L-arabinoside (0·08 g.) was isolated. Chromatography showed that no sugars other than derivatives of L-arabinose were present.

Action of Lithium Aluminium Hydride on Methyl 2 : 3 : 4-*Tri*-O-*acetyl*-β-L-*arabinoside*.—Powdered methyl tri-*O*-acetyl-β-L-arabinoside (2 g.) was added to an ice-cold suspension of lithium aluminium hydride (6·3 g.) in ether (350 c.c.), and the mixture was heated under reflux for 24 hr. The product, isolated in the usual way, was methyl β-L-arabinoside (0·68 g., 61%), m. p. and mixed m. p. 169—170°.

The authors thank Professor M. Stacey, F.R.S., for his interest and encouragement. This work was supported by a grant from Imperial Chemical Industries Limited.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

[*Received, March 27th*, 1954.]

Deoxy-sugars. Part XXVII. The Catalytic Oxidation of Some Derivatives of 2-Deoxy-D-hexoses.*

By W. G. Overend, F. Shafizadeh, M. Stacey, and G. Vaughan.

[Reprint Order No. 5245.]

Overend, Shafizadeh, and Stacey (*J.*, 1951, 1487) described the preparation of some derivatives of 2-deoxy-D-galacturonic acid from methyl 2-deoxy-3 : 4-*O*-*iso*propylidene-α-D-galactoside by oxidation with alkaline potassium permanganate. We now describe the selective oxidation of 2-deoxy-sugars in alkaline solution by gaseous oxygen in the presence of platinum black (cf. Fernández-Garcia, Amarós, Blay, Santiago, Soltero-Diaz, and Colón, *El Crisol* (*Puerto Rico*), 1950, **4**, 40; *Chem. Abs.*, 1951, **45**, 555; Barker, Bourne, and Stacey, *Chem. and Ind.*, 1951, 970; Marsh, *Nature*, 1951, **168**, 602; Mehltretter, Alexander, Mellies, and Rist, *J. Amer. Chem. Soc.*, 1951, **73**, 2424).

Methyl 2-deoxy-α-D-glucopyranoside thus afforded methyl 2-deoxy-α-D-glucosiduronic acid which was converted through the methyl ester into the crystalline amide. Likewise, crystalline methyl 2-deoxy-α-D-galactosiduronamide was prepared from methyl 2-deoxy-α-D-galactopyranoside. Attempts to oxidise methyl 2-deoxy-αβ-D-ribofuranoside by this method were inconclusive : oxidation occurred, but the labile sugar also partly decomposed and the product was impure. 2-Deoxy-D-glucose gave a crystalline 2-deoxy-D-glucarodilactone (cf. Overend *et al.*, *loc. cit.*, for the oxidation of 2-deoxy-D-galactose with dinitrogen tetroxide, and of 2-deoxy-D-galacturonic acid with bromine, procedures which afford a monolactone of 2-deoxy-D-galactaric acid). This dilactone, presumably the 1 : 4-3 : 6-dilactone, reduced Fehling's solution and in alkaline solution had a strong absorption band at 212 mμ., which was modified on acidification. In these respects it resembles the dilactones of D-glucaric and D-mannaric acid (Smith, *J.*, 1944, 510, 571, 634; Heslop and Smith, *J.*, 1944, 575, 638; Haworth, Heslop, Salt, and Smith, *J.*, 1944, 217) and so presumably undergoes the same type of isomerization.

Experimental.—Methyl 2-deoxy-α-D-glucosiduronamide. A gentle stream of pure oxygen was passed through a solution of methyl 2-deoxy-α-D-glucopyranoside (2 g.) and potassium hydrogen carbonate (3 g.) in water (250 c.c.) at 55°. Platinised charcoal (1·4 g.; 13% of Pt) was added and the solution was stirred mechanically. After one week when reaction was complete as indicated by passing the excess of oxygen through barium hydroxide solution (no more carbon dioxide), the mixture was filtered and evaporated to dryness. The residue was extracted with dry methanol, and after concentration of the extract to 10 c.c., methyl iodide (10 c.c.) was added, and the whole was heated under reflux for 7 hr. After evaporation, the product was extracted with ethyl acetate. The residue from this extraction was re-treated with methyl iodide, and the above procedure was repeated thrice, until a residue was obtained which gave only a very weak Tollens test for uronic acids. The combined ethyl acetate extracts were evaporated and the crude product was dissolved in dry methanol which had been saturated at 0° with ammonia. After being kept at 0° for 18 hr., the mixture was evaporated and afforded a crystalline residue, which was recrystallised from methanol. *Methyl 2-deoxy-α-D-glucopyranosiduronamide* (0·74 g., 34·4%) was obtained as colourless prisms, m. p. 192°, $[\alpha]_D^{19}$ +119·6° (*c*, 0·81 in MeOH) (Found : C, 44·1; H, 6·8; N, 7·4. $C_7H_{13}O_5N$ requires C, 44·0; H, 6·8; N, 7·3%). It gave a strong positive test for uronic acid with Tollens naphtharesorcinol reagent. Hydrolysis afforded only a syrup.

Methyl 2-Deoxy-α-D-galactosiduronamide. Methyl 2-deoxy-α-D-galactopyranoside (1·2 g.) and potassium hydrogen carbonate (1·6 g.) and 13% platinised charcoal (0·7 g.) in water (200 c.c.) were treated with pure oxygen for 8 days at 60°. Reaction was then complete and the mixture was worked up as described above. Methyl 2-deoxy-α-D-galactosiduronamide (0·3 g., 26·7%) had m. p. 202°, $[\alpha]_D^{16}$ +104° (*c*, 1·01 in MeOH) (Found : C, 44·1; H, 6·6; N, 7·2. Calc. for $C_7H_{13}O_5N$: C, 44·0; H, 6·8; N, 7·3%). Overend *et al.* (*loc. cit.*) report m. p. 203°, $[\alpha]_D$ +105·4° in MeOH.

2-Deoxy-D-glucosaccharodilactone (*2-deoxy-D-glucaric dilactone*). 2-Deoxy-D-glucose (2·5 g.) and potassium hydrogen carbonate (3·5 g.) in water (250 c.c.) were oxidised in the presence of platinum black as above. The filtered mixture was then passed through Amberlite IR–120

* Part XXVI, preceding paper.

(H), the effluent evaporated to dryness, and the residue extracted with hot ethyl acetate (300 c.c.). Evaporation of the extract afforded a syrup which crystallised on trituration with methanol. On recrystallisation from ethyl acetate 2-*deoxy*-D-*glucarodilactone* (0·71 g., 29·6%) formed colourless needles, m. p. 139·5°, $[\alpha]_D^{25}$ +170° (*c*, 0·48 in MeOH) (Found: C, 45·9; H, 4·0. $C_6H_6O_5$ requires C, 45·6; H, 3·8%). It strongly reduced Fehling's solution and in 0·1N-sodium hydroxide exhibited absorption at 212 mμ. (ε 10,000) which was modified on acidification.

This investigation was supported by a grant from the British Empire Cancer Campaign (Birmingham Branch).

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM 15.

[*Received, March 26th,* 1954.]

Solubility and Chromatography of Hydroxybenzoic Acids.

By P. A. ONGLEY.

[Reprint Order No. 5272.]

MANY physiologically active compounds are chelated (cf. Davies, *Chem. and Ind.*, 1953, 614),* and because of the far greater antirheumatoid activity of 2 : 6-dihydroxybenzoic acid, than of the 2-mono- and of the 2 : 5-di-hydroxy-acid (Reid, Watson, Cochran, and Sproull, *Brit. Med. J.*, 1951, II, 321), the state of the 2 : 6-acid was studied. Since 2-nitroresorcinol (Baker, *J.*, 1933, 687; Hilbert, Wulf, Hendricks, and Liddell, *J. Amer. Chem. Soc.*, 1936, **58**, 548), 1 : 8-dihydroxyanthraquinone, and 2 : 2′-dihydroxybenzophenone are all dichelated (Hilbert, Wulf, Hendricks, and Liddell, *loc. cit.*), dichelation in 2 : 6-dihydroxybenzoic acid would not be surprising. Although Baker (*Nature*, 1936, **137**, 236) suggested that the very low pK_a of the acid may well be due to dichelation, the problem has never been thoroughly investigated.

The low solubility of hydroxybenzoic acids in non-polar solvents precludes any comparative examination of spectra, either of different acids in these solvents or of the same acid in polar and non-polar solvents, (cf. the work of Morton and Stubbs, *J.*, 1940, 1347) on the hydroxy-benzaldehydes and -acetophenones. Comparison of partition ratios (from which may be deduced data on the dissociation of the dimeric to the monomeric acids, cf. Moelwyn-Hughes, *J.*, 1940, 850) is likewise impossible. It was therefore decided to compare the solubilities of benzoic acid and various hydroxy- and methoxy-derivatives in several solvents. Although these data can only give a summation of the variations in ΔS and ΔH, and more information would be obtainable by calculating H from solubilities at several temperatures, the results so far obtained are sufficiently significant to merit being recorded.

p*S values of substituted benzoic acids in various solvents.*

	H_2O	N-NaCl	N-Salt *	C_6H_6	$CHCl_3$	CCl_4	*cyclo*Hexane
Benzoic acid	1·556	1·714	1·372	0·118	−0·188	0·291	1·038
o-Hydroxy-	1·793	1·991	1·413	1·239	0·680	1·644	2·192
m-Hydroxy-	1·275	1·422	—	3·198	2·629	4·699	>6·000
p-Hydroxy-	1·370	1·530	—	3·432	2·991	5·000	4·398
2 : 4-Dihydroxy-...	1·493	1·517	—	2·412	1·897	5·301	5·000
2 : 5-Dihydroxy-...	0·845	0·991	—	3·403	1·900	>6·000	>6·000
2 : 6-Dihydroxy-...	1·261	1·714	1·085	1·896	0·539	2·556	3·627
3 : 4-Dihydroxy-...	1·068	1·188	—	>6·000	3·311	4·398	>6·000
o-Methoxy-	1·507	1·672	—	0·674	−0·225	1·605	1·241
m-Methoxy-	1·028	1·195	—	0·398	−0·049	0·737	1·851
p-Methoxy-	2·620	2·979	—	1·714	1·130	—	—
2 : 6-Dimethoxy-	1·638	1·695	—	1·796	0·697	—	4·000

* N-Solution of the sodium salt of the benzoic acid.

Experimental.—The acids were either of "AnalaR" standard or were recrystallized before use. Solubilities were measured by rotating tubes of solvent and solute for at least 8 hr. at

* In this communication the term "chelation" is used in the restricted sense of intramolecular hydrogen bonding and not in the wider sense suggested by Rolla (*Gazzetta*, 1948, **78**, 316).

25° (preliminary experiments showed that saturation is reached in 2 hr.). The solutions were concentrated, if necessary, and were titrated with standard alkali, bromothymol-blue–neutral-red being used as mixed indicator.

Experimental values of solubilities are recorded in the Table. A new method of reporting them has been adopted. They are expressed as the negative logarithms (pS values) of the concentrations in the saturated solutions in moles per litre, by analogy with pH values.

Discussion.—Consideration of these results indicate that: 1. Values for the methoxy-acids show that there is no significant difference between the 2- and the 2 : 6-acid on the one hand and the 3- and the 4-acid on the other. From this it is evident that there is no steric effect, nor has the weak chelation of the former acids any effect. 2. The solubility in water, N-sodium chloride solution, and a normal solution of the salt of the particular acid is virtually uninfluenced by chelation. 3. In the non-polar solvents an acid containing an intermolecular bonded ("free") hydroxy-group is far less soluble than either the chelated isomer or the corresponding methoxy-acid. 4. 2 : 6-Dihydroxybenzoic acid behaves as an acid containing no free hydroxyl group. This is in agreement not only with the pK evidence cited by Baker (*loc. cit.*), but also with that from chromatographic adsorption (see below) and from infra-red spectra (Davies, private communication).

Chromatography of Hydroxybenzoic Acids.—Hoyer (*Kolloid Zeit.*, 1950, **116**, 121) stated that if a substance containing a hydroxy-group is passed in solution through such an adsorbent as silica, whether or not the substance is adsorbed on the column depends on whether the hydroxy-group is free or chelated. Although chelation prevents adsorption, intermolecular hydrogen bonding does not.

Solutions of the hydroxybenzoic acids in chloroform (0·0100M for benzoic, and 2-mono- and 2 : 6-dihydroxybenzoic acids, and saturated for the other acids) were passed down columns of activated silica. To obtain conditions as uniform as possible (*a*) the same batch of activated silica was used throughout; (*b*) 1·00 g. of silica was always used and was always packed in glass tubing of the same bore; (*c*) the amount of acid adsorbed was estimated by titrating the first 10·0-ml. sample; and (*d*) the time of flow was approximately constant. All determinations were carried out in quadruplicate, and the results were quite concordant. % Adsorptions are: benzoic acid, 55·0; *o*-hydroxy-, 28·0; *m*-hydroxy-94·2; *p*-hydroxy-, 97·8; 2 : 4-dihydroxy-, 87·2; 2 : 6-dihydroxy-, 61·0; and 3 : 4-dihydroxy-benzoic acid, 78·6.

If allowance is made for adsorption due to the carboxyl-group, these results clearly corroborate Hoyer's assertion. The somewhat low value for the 3 : 4-acid is possibly due to the weak chelation between the hydroxyl groups lessening but not abolishing hydroxyl-adsorption. The value for the 2 : 6-acid confirms its dichelation. It would seem, however, that the chelation of the second hydroxy-group is somewhat weaker.

This work was done during the tenure of a Medical Research Council grant. I thank sincerely Dr. J. C. Speakman of the University of Glasgow and Dr. M. M. Davies of the University College of Aberystwyth for their helpful discussions of this work.

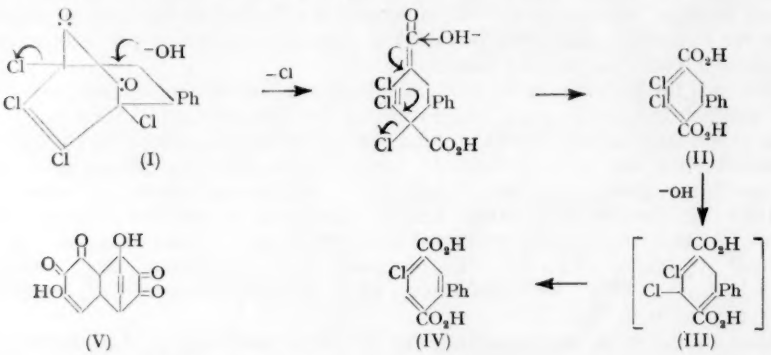
UNIVERSITY OF GLASGOW.
[*Present address*: BIRKENHEAD TECHNICAL COLLEGE, BIRKENHEAD.] [*Received, April 1st*, 1954.]

A Base-catalysed Rearrangement, of Non-benzilic Acid Type, of a Bridged α-Diketone.

By R. H. Burnell and W. I. Taylor.

[Reprint Order No. 5355.]

Horner and Merz (*Annalen*, 1950, **570**, 89) showed that the adduct (I), formed from tetrachloro-*o*-benzoquinone by a Diels–Alder reaction, is smoothly converted by warm 2N-sodium hydroxide into a dicarboxylic acid to which structure (III) was assigned, and by more vigorous treatment into the diphenyl derivative (IV) which with concentrated sulphuric acid yielded the known 3-carboxy-2-chlorofluorenone. Although Horner and Merz stated that there was no known analogy for this isomerisation and although the ultra-violet absorption spectrum of the acid (III) (see curve 3) did not, as it should, resemble that of *cis*-cinnamic acid (curve 1), these authors made no further comment. Consideration of the stereochemistry of the adduct (I) led us to conclude that the action of alkali would lead to the acid (II) rather than to (III), according to the annexed scheme. This structure, containing vinyl chloride groups, is in better agreement with the known stability to alkali, for formation of the diphenyl (IV) is slow. The ultra-violet absorption spectrum of (II), either as the acid or its dimethyl ester (curve 3), shows a maximum almost identical with



that of dimethyl *cyclo*hexa-1 : 3-diene-1 : 4-dicarboxylate (curve 2), the lower value for ε being ascribed to steric inhibition of resonance between the homoannular diene and the 4-carboxy-group between the 3-chloro- and the 5-phenyl substituent (cf., for example, steric inhibition of resonance in substituted diphenyls). The conversion of the dichloro-acid (II) by strong alkali into the diphenyl (IV) is thought to proceed *via* (III) although we have been unable to isolate this, probably owing to its ready conversion into (IV). Baeyer (*Annalen*, 1889, **251**, 257; 1890, **258**, 1) showed that alkaline isomerisation of *cyclo*hexa-diene-1 : 4-dicarboxylic acid yielded finally *cyclo*hexa-1 : 4-diene-1 : 4-dicarboxylic acid, which further supports the postulated intermediacy of (III) in the above scheme.

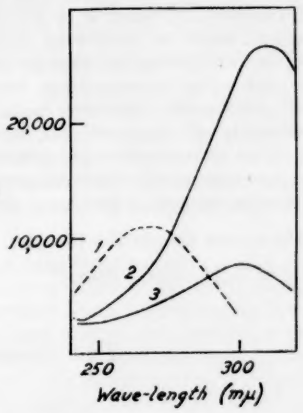
The adduct from tetrabromo-*o*-benzoquinone and phenylacetylene gave no homogeneous material on treatment with alkali. The results of this work support criticisms made by Cook and Loudon (*Quart. Reviews*, 1951, **5**, 99) against a suggestion that (V) was a precursor of purpurogallin, formed by a Diels–Alder reaction between two molecules of 3-hydroxy-*o*-benzoquinone. We were unable to add isoprene to 3-hydroxy-*o*-benzoquinone.

Experimental.—Adducts were prepared according to Horner and Merz's procedure (*loc. cit.*).

2 : 3-*Dichloro*-5-*phenyl*cyclo*hexa*-1 : 3-*diene*-1 : 4-*dicarboxylic acid* (II). The adduct prepared from styrene and tetrachloro-*o*-benzoquinone was warmed at 40° with 2N-sodium hydroxide for 1 hr., then acidified to furnish the *cyclo*hexadiene acid, m. p. 235° (from methanol–water) (Found : C, 53·7; H, 3·3. Calc. for $C_{14}H_{10}O_4Cl_2$: C, 53·7; H, 3·2%); absorption max. (curve 3) 302 mμ (ε = 7400 in EtOH), and 1705 (C=O) and 1685 cm.$^{-1}$. The dimethyl ester had m. p. 78° (from methanol–water) (Found : C, 56·4; H, 4·2. Calc. for $C_{16}H_{14}O_4Cl_2$: C, 56·3;

H, 4·1%); the absorption in EtOH was identical with that of the parent acid; infra-red max. were at 1728 (C=O) and 1710 cm.$^{-1}$. The adduct was also converted into (II) during 2 hr. at 60° in sodium carbonate solution. Sodium hydrogen carbonate was also effective but required more than a day at 60°. The adduct was recovered largely unchanged after being heated with sodium acetate or dilute sulphuric acid although small amounts of highly coloured material were slowly formed.

*Dimethyl*cyclo*hexa*-1 : 3-*diene*-1 : 4-*dicarboxylate*. *cyclo*Hexa-1 : 3-diene-1 : 4-dicarboxylic acid (Baeyer, *Annalen*, 1889, **261**, 301) with diazomethane furnished the pure ester, m. p. 81° (from methanol) (Found : C, 60·5; H, 6·3. Calc. for $C_{10}H_{12}O_4$: C, 61·2; H, 6·2%); absorption max. 309 mμ (ε = 27,300 in EtOH) (curve 2) and 1715 cm.$^{-1}$ (C=O).



1, cis-*Cinnamic acid*.
2, *Dimethyl* cyclo*hexa*-1 : 3-*diene*-1 : 4-*dicarboxylate*.
3, 2 : 3-*Dichloro*-5-*phenyl*cyclo*hexa*-1 : 3-*diene*-1 : 4-*dicarboxylic acid or its dimethyl ester*.

1 : 2 : 3 : 4-*Tetrabromo*-5 : 6-*dioxo*-8-*phenyl*bicyclo(2 : 2 : 2)*octa*-2 : 7-*diene*. Prepared from tetrabromo-*o*-benzoquinone and phenylacetylene, the adduct melted at 172° (from methanol). Even after many crystallisations we were unable to prepare an analytically pure sample (Found : C, 34·3; H, 1·3. Calc. for $C_{14}H_6O_2Br_4$: C, 32·0; H, 1·2%). The adduct was stable in water or dilute sulphuric acid but readily decomposed in hot sodium acetate, warm sodium carbonate, or sodium hydroxide solution.

We are indebted to the National Research Council of Canada for a grant and to Mr. W. Fulmor and staff, American Cyanamide Co., Lederle Laboratories Division, for determination of the infra-red spectra.

CHEMICAL LABORATORIES, UNIVERSITY OF NEW BRUNSWICK. [*Received, May 5th*, 1954.]

The Compound of Antimony Pentachloride with Nitric Oxide.

By H. J. M. BOWEN.

[Reprint Order No. 5358.]

A COMPOUND of antimony pentachloride with nitric oxide was originally described by Besson (*Compt. rend.*, 1889, **108**, 1012) and given the formula $(SbCl_5)_2NO_2$. It is clear that Besson was using the wrong equivalent for oxygen (his formula for nitrogen dioxide is NO_4), but if the compound is correctly designated by $(SbCl_5)_2NO$ it should be paramagnetic. This deduction has now been tested.

Experimental.—Commercial antimony pentachloride was vacuum-distilled into Pyrex reaction vessels immediately before each run : distilled specimens melted at 1·8—2·2°. Nitric oxide, prepared by Johnston and Giauque's method (*J. Amer. Chem. Soc.*, 1929, **51**, 3194), was stored over phosphoric oxide in a reservoir flask. When it was condensed on to the solid antimony pentachloride at —196°, an intense purple colour, which vanished above —140°, developed at the interface. The mixture was allowed to warm to room temperature and

then further warmed to break up the surface crust of solid adduct formed. Several condensations were necessary before the reaction was tolerably complete. Excess of the reactants was then removed by continued pumping at room temperature, and the product was finally sealed off *in vacuo*. When the sealed tubes were heated at 100° for some time the compound crystallised in lemon-yellow plates, as observed by Besson (*loc. cit.*). Analysis was carried out by breaking a weighed tube of the sample, sealed *in vacuo*, under mercury, and heating it to approx. 240° until no more nitric oxide was evolved. The volume of the nitric oxide was measured and the chloride in the residue was determined by Volhard's method [Found: NO, 4·74; Cl, 55·9. $(SbCl_5)_2NO$ requires NO, 4·77; Cl, 56·4%. Calc. for $SbCl_5,NO$: NO, 9·11; Cl, 53·9%].

The magnetic susceptibility of the *compound* was measured at room temperature by Dr. J. K. Dawson and found to be less than 3×10^{-7} c.g.s. units/g. Hence the true formula of the compound must be some even multiple of $(SbCl_5)_2NO$. The substance sublimes at 100° *in vacuo*, but an attempt to measure the molecular weight by Victor Meyer's method gave a low value, indicating decomposition, which was in fact observed. The substance was insoluble in liquid nitric oxide, antimony pentachloride, and carbon tetrachloride, and reacted more or less violently with water, alcohol, acetone, ether, *iso*pentane, benzene, and chloroform. Sodium-dried ether gave a white precipitate, presumably of $SbCl_5,Et_2O$ (cf. Williams, *Ber.*, 1876, **9**, 1135), and sodium-dried benzene gave red and violet precipitates, soluble in excess of the solvent, in the same manner as antimony pentachloride itself (Hilpert and Wolf, *Ber.*, 1913, **46**, 2215).

The author thanks the Director, A.E.R.E., for permission to publish this note.

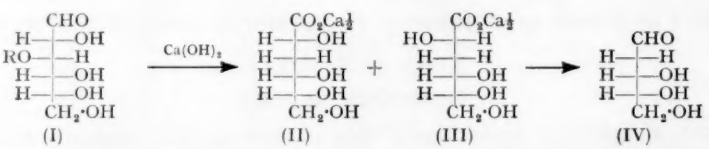
A.E.R.E., Harwell, Berks. [*Received, May 5th,* 1954.]

The Preparation of 2-Deoxy-D-ribose.

By G. N. Richards.

[Reprint Order No. 5364.]

The preparation of 2-deoxy-D-ribose has received much attention (see, *e.g.*, Overend and Stacey, *J. Sci. Food Agric.*, 1950, **1**, 168) but the glycal method, as modified by Deriaz, Overend, Stacey, Teece, and Wiggins (*J.*, 1949, 1879), remained the most satisfactory, affording 10% yields from D-arabinose. Now, however, the calcium salts of Nef's mixed glucometasaccharinic acids (*Annalen*, 1910, **376**, 1) are conveniently accessible by the action of lime-water on, *e.g.*, 3-*O*-methyl-D-glucose (I; R = Me) (Kenner and Richards, *J.*, 1954, 278), itself readily prepared in 60% yield (Glen, Myers, and Grant, *J.*, 1951, 2568) from D-glucose. These salts may be prepared from the 1 : 3-linked polysaccharide laminarin (Corbett, Kenner, and Richards, *Chem. and Ind.*, 1953, 462; Corbett and Kenner, *J.*, 1954, 3274), or from any other 3-*O*-substituted glucose, mannose, or fructose derivative (patent pending).



The structure suggested by Nef (*loc. cit.*) for the acids indicated that application of Ruff's method of degradation (*Ber.*, 1901, **34**, 1362) of either of the calcium glucometasaccharinates (II, III) should yield 2-deoxy-D-ribose (IV), and in fact by this procedure, as modified by Fletcher, Diehl, and Hudson (*J. Amer. Chem. Soc.*, 1950, **72**, 4546), either salt or the mixture of the two obtained directly by lime-water degradation of 3-*O*-methyl-D-glucose, afforded 2-deoxy-D-ribose in 30—35% yield. The amorphous product was found by paper chromatography to contain only traces of impurities and corresponded to authentic samples of 2-deoxy-D- and -L-ribose kindly supplied by Professor M. Stacey and by Dr. G. W. Kenner. Crystallisation occurred slowly on trituration with *iso*propanol, and the product was readily characterised as its aniline derivative. Other derivatives,

described in the Experimental section, were readily prepared from either amorphous or recrystallised 2-deoxy-D-ribose and it is suggested that the syrupy product obtained directly from the degradation is sufficiently pure for most synthetic work.

The fact that the isomeric glucometasaccharinic acids differ only in their configuration about $C_{(2)}$ was thereby confirmed, but the definite assignment of configuration to the α- and β-isomerides (II, III) requires knowledge of the orientation of the 2-hydroxyl group. The suggestion made previously (Kenner and Richards, *loc. cit.*) has been confirmed by the demonstration of the identity of β-glucometasaccharinolactone with 3-deoxy-γ-D-mannonolactone (from III), which was obtained by hydrolysis, and subsequent oxidation with bromine, of authentic methyl 3-deoxy-α-D-mannoside. The γ-lactone structure is proposed on the basis of the absence of mutarotation in an aqueous solution of the compound. It is reasonable to assume from the mechanism of saccharinic acid formation (Kenner *et al.*, *J.*, 1954, 278; 1953, 2245) that the corresponding α-isomer is the lactone of 3-deoxy-D-gluconic acid (from II).

Almost simultaneously with our earlier announcement (*Chem. and Ind.*, 1953, 1035), Sowden (Amer. Chem. Soc., 124th Meeting, 1953, Sept., 15D) reported that, from the crude mixture of saccharinic acids obtained directly by action of sodium hydroxide on glucose (Nef, *loc. cit.*), he had isolated an amorphous product which required purification through the benzylphenylhydrazone before crystallisation of the 2-deoxy-D-ribose was effected.

Experimental.—*2-Deoxy-D-ribose.* Barium acetate (1·15 g.) and ferric sulphate (0·60 g.) were added to a warm solution of the mixed calcium salts of 3-deoxy-D-mannonic and 3-deoxy-D-gluconic acids (10·01 g.; obtained by the action of lime-water on 3-*O*-methyl-D-glucose; Kenner and Richards, *loc. cit.*). The solution was heated to boiling and filtered, the precipitate being washed with boiling water (2 × 10 ml.). The combined filtrate and washings were cooled to 40° and hydrogen peroxide (7 ml.; 30%) added. After a short induction period the temperature of the solution rose to 70° and gas evolution occurred. The mixture was left to cool to 40°, then more hydrogen peroxide (7 ml.; 30%) was added, the temperature subsequently rising to 50°. The pressure in the flask was next reduced to 25 mm. and a slow stream of air drawn through the solution to decompose bicarbonates. After cooling to room temperature under these conditions the solution was filtered and stirred successively with Amberlite resins IR-120 (20 g.) for 15 min. and IR-4B (50 g.) for 1 hour. Deionisation of the solution was completed by standing over a mixture of the above resins (10 and 20 g. respectively) overnight. Evaporation of the solution then yielded a colourless syrup (2·12 g., 31·6%) which was shown by paper chromatography (alkaline silver nitrate spray; Trevelyan, Procter, and Harrison, *Nature*, 1950, **166**, 444) to be almost pure 2-deoxy-D-ribose (R_F 0·525; in butanol–pyridine–water, 3 : 2 : 1·5). The syrup crystallised slowly on trituration with dry *iso*propanol, and when repeatedly recrystallised from the same solvent mixed with ether, showed m. p. 90—92°, $[\alpha]_D^{21}$ −80° (5 min.) ⟶ −44° (24 hr., equil.) (*c*, 2 in MeOH) (Found: C, 44·6; H, 7·6. Calc. for $C_5H_{10}O_4$: C, 44·8; H, 7·5%). Deriaz *et al.* (*loc. cit.*) report m. p. 96—98°, $[\alpha]_D^{20}$ −93° (4 min.) ⟶ −46° (24 hr., equil.) (*c*, 6 in MeOH), for 2-deoxy-β-D-ribose.

Derivatives of 2-deoxy-D-ribose. 2-Deoxy-D-ribose (amorphous or crystalline) yielded in the usual manner colourless needles of the aniline derivative (60—70%), m. p. 171·5—173°, $[\alpha]_D^{20}$ +17·4° (*c*, 0·4 in EtOH) (Found: C, 62·9; H, 7·4; N, 6·8. Calc. for $C_{11}H_{15}O_3N$: C, 63·1; H, 7·2; N, 6·7%). Overend, Stacey, and Wiggins (*J.*, 1949, 1358) reported m. p. 174—175°, $[\alpha]_D^{22}$ +19·5°.

2-Deoxy-D-ribose (0·15 g.) and *p*-toluidine (0·12 g.) were dissolved, with warming, in ethanol (2 ml.) and the solution kept at room temperature overnight. White needles of *N-2-deoxy-D-ribosyl-p-toluidine* (0·20 g.) separated and after recrystallisation from ethanol had m. p. 167—168° (Found: N, 6·1. $C_{12}H_{17}O_3N$ requires N, 6·3%).

2-Deoxy-D-ribose (0·10 g.) in ethanol (2 ml.) was heated under reflux for 1½ hr. with 2 : 4-dinitrophenylhydrazine (0·14 g.). Addition of water then precipitated the *2 : 4-dinitrophenylhydrazone* as a yellow powder, m. p. 127—128° after crystallisation from ethanol–water (Found: N, 18·2. $C_{11}H_{14}O_7N_4$ requires N, 17·8%).

3-Deoxy-D-mannonolactone. A solution of methyl 3-deoxy-α-D-mannoside (0·65 g.; prepared according to Bollinger and Prins, *Helv. Chim. Acta*, 1946, **29**, 1061) in N-sulphuric acid (10 ml.) was heated on the boiling-water bath to constant rotation (3 hr.; $[\alpha]_D^{20}$ −12·4°). After neutralisation with barium carbonate, 3-deoxy-D-mannose was isolated in the usual way as a colourless

syrup (0·522 g., 87%), $[\alpha]_D^{20}$ −13·5° (*c*, 5 in H_2O) (Found: C, 44·3; H, 7·3. Calc. for $C_6H_{12}O_5$: C, 43·9; H, 7·4%). Bollinger and Prins (*loc. cit.*) reported $[\alpha]_D^{14}$ +17·7° for this compound, and it is intended to discuss this discrepancy in a later paper.

A solution of the amorphous product (0·502 g.) in water (5 ml.) was treated with bromine (0·5 ml.) at room temperature for 3 days and 3-deoxy-D-mannonic acid was isolated in the usual way as a pale yellow syrup (0·417 g.). When dried for several days over phosphoric oxide, 3-deoxy-γ-D-mannonolactone crystallised slowly, and when recrystallised from acetone showed m. p. 89—90°, alone or on admixture with β-D-glucometasaccharinolactone obtained from 3-*O*-methyl-D-glucose (Kenner and Richards, *loc. cit.*), $[\alpha]_D^{20}$ +8·0° (*c*, 2 in H_2O) unchanged after 24 hr. at room temperature (Found: C, 44·6; H, 6·3. Calc. for $C_6H_{10}O_5$: C, 44·4; H, 6·2%). Bollinger and Prins (*loc. cit.*) describe this compound as amorphous.

The author is grateful to Professor J. Kenner, F.R.S., for his interest and advice and to Professor M. Stacey, F.R.S., who directed earlier work on the degradation of calcium 3-deoxy-D-mannonate. This work forms part of the programme of fundamental research undertaken by the Council of the British Rayon Research Association.

British Rayon Research Association, Heald Green Laboratories,
Wythenshawe, Manchester. [*Received, May 5th*, 1954.]

Preparation of neo*Pentyl Chloride.*

By W. Gerrard and P. Tolcher.

[Reprint Order No. 5400.]

*neo*Pentyl chlorosulphinate is readily prepared by the interaction of the alcohol and thionyl chloride (Gerrard, Nechvatal, and Wilson, *J.*, 1950, 2088) but, compared with chlorosulphinates of ordinary alcohols such as butan-1-ol or octan-2-ol, has remarkable thermal stability. Earlier attempts to catalyse the decomposition by means of pyridine hydrochloride were only partly successful, because the requirements of time and temperature were inadequately met. By heating the chlorosulphinate at 115° for 24 hr. in the presence of quinoline hydrochloride we have obtained *neo*pentyl chloride in 47% yield.

Our observation is relevant to a recent paper by Sommer, Blankman, and Miller (*J. Amer. Chem. Soc.*, 1954, **76**, 803), in which is described the formation of *neo*pentyl chloride from a mixture of *neo*pentyloxytriethylsilane, thionyl chloride, and quinoline hydrochloride heated at 115° for 23 hr. However, in the course of other work we found that *neo*pentyloxytrimethylsilane reacted readily with thionyl chloride alone to give *neo*pentyl chlorosulphinate.

$$Me_3Si{\cdot}O{\cdot}C_5H_{11} + SOCl_2 \longrightarrow Me_3SiCl + C_5H_{11}O{\cdot}SOCl$$

From this it appears that in the experiment of Sommer *et al.* the alkyl chloride was really coming from the chlorosulphinate.

Experimental.—neo*Pentyloxytrimethylsilane*, b. p. 121—122°, n_D^{20} 1·3934, d_4^{20} 0·7632 (Found: C, 60·7; H, 12·9. $C_8H_{20}OSi$ requires C, 60·0; H, 12·5%), was prepared by the addition of trimethylchlorosilane (1 mol.) to *neo*pentyl alcohol (1 mol.) and pyridine (1 mol.) in ether (160 c.c.) at −10°. Thionyl chloride (12·8 g., 1 mol.) was added to the silane (8·6 g., 0·5 mol.) at 15°, and after 10 min. excess of thionyl chloride was removed at 15°/20 mm. *neo*Pentyl chlorosulphinate (6·9 g., 75%), b. p. 62—66°/20 mm., n_D^{20} 1·4520 (Found: Cl, 20·5. Calc. for $C_5H_{11}O_2ClS$: Cl, 20·8%), and di*neo*pentyl sulphite (1·1 g., 18·6%), b. p. 110°/19 mm., n_D^{20} 1·4316, were obtained. When thionyl chloride (6·61 g., 1 mol. instead of 2 mols.) was used with the silane (8·9 g., 1 mol.) trimethylchlorosilane (5·6 g., 92%), b. p. 55—58° (Found: Cl, 33·7. Calc. for C_3H_9ClSi: Cl, 32·7%), was also isolated; but the yield of chlorosulphinate (2·2 g., 23%) b. p. 66—74°/20 mm., n_D^{20} 1·4501, was reduced, whereas that of the sulphite (3·5 g., 56%), b. p. 98—100°/12 mm., n_D^{20} 1·4300, increased.

Decomposition of neo*pentyl chlorosulphinate in the presence of quinoline hydrochloride.* The chlorosulphinate (prepared from alcohol and thionyl chloride) (15·0 g., 1 mol.) was mixed with the hydrochloride (0·3 g., 0·03 mol.) and heated at 115° for 24 hr. Volatile products were removed at 15°/15 mm. and collected at −80°. The condensate (6·2 g.) contained easily

hydrolysable chlorine (5·6%) representing 17% of *tert.*-amyl chloride, and the latter was removed by 2N-nitric acid (3 × 20 c.c.). After being washed with water and dried, the product afforded *neo*pentyl chloride (4·4 g., 47%), b. p. 82·5°, n_D^{20} 1·4048 (Found: C, 56·6; H, 10·25; Cl, 33·25. Calc. for $C_5H_{11}Cl$: C, 56·35; H, 10·3; Cl, 33·3%). The product did not contain easily hydrolysable chlorine.

THE NORTHERN POLYTECHNIC,
HOLLOWAY ROAD, LONDON, N.7.

[*Received, May 21st*, 1954.]

Crystalline 1-*Benzoyl*-1 : 2-*dihydroquinoline.*

By R. F. COLLINS.

[Reprint Order No. 5407.]

DURING an investigation requiring the preparation of derivatives related to the Reissert compound, which is considered to be 1-benzoyl-2-cyano-1 : 2-dihydroquinoline, a pure sample of 1-benzoyl-1 : 2-dihydroquinoline was required. This compound has been described as an oil by Johnson and Buell (*J. Amer. Chem. Soc.*, 1952, **74**, 4517) and by Rosenmund and Zymalkowski (*Chem. Ber.*, 1953, **86**, 37). It has now been obtained crystalline, is quite stable, and provides a useful reference derivative for the unstable 1 : 2-dihydroquinoline. A sample of freshly prepared 1 : 2-dihydroquinoline was observed to change to a brown oil when stored in a vacuum-desiccator over silica gel.

The structure of the crystalline benzoyl derivative was confirmed by hydrogenation over platinum to the known 1-benzoyl-1 : 2 : 3 : 4-tetrahydroquinoline (Johnson and Buell, *loc. cit.*). Acid hydrolysis of 1-benzoyl-1 : 2-dihydroquinoline yielded 67% of benzoic acid and a basic brown oil with the characteristic odour of 1 : 2-dihydroquinoline. This is in contrast to 1-benzoyl-2-cyano-1 : 2-dihydroquinoline which yields benzaldehyde on acid hydrolysis.

Experimental.—For 1 : 2-dihydroquinoline Bohlmann (*Chem. Ber.*, 1952, **85**, 390) gives m. p. 40—41°. Our specimen, prepared by his method but extracted with light petroleum (b. p. 40—60°) and crystallised at −80°, had m. p. 62—65°.

1 : 2-Dihydroquinoline (4 g.), freshly isolated and purified, in freshly distilled pyridine (15 ml.) was treated slowly with benzoyl chloride (5 ml.) in pyridine (5 ml.) at <10°, then with more benzoyl chloride (5 ml.) at <15°. The mixture was then left for 24 hr. at room temperature. Addition of water, extraction with ether, washing with dilute hydrochloric acid, water, and aqueous sodium hydroxide, drying, and evaporation gave an oil which was repeatedly extracted with light petroleum (b. p. 40—60°). The product (4·8 g.), m. p. 84—87°, crystallised on concentration and cooling to −80°. Recrystallisation from ethyl alcohol yielded pure 1-benzoyl-1 : 2-dihydroquinoline (3·1 g.), m. p. 89° (Found: C, 81·8; H, 5·7; N, 5·9. Calc. for $C_{16}H_{13}ON$: C, 81·7; H, 5·5; N, 5·95%).

Hydrogenation of this (0·6 g.) in ethyl alcohol (20 ml.) over platinum oxide (0·05 g.) gave 1-benzoyl-1 : 2 : 3 : 4-tetrahydroquinoline (0·45 g.), m. p. 74—75° (cf. Johnson and Buell, *loc. cit.*) (Found: C, 80·8; H, 6·37; N, 6·0. Calc. for $C_{16}H_{15}ON$: C, 81·0; H, 6·3; N, 5·9%). The quantity of hydrogen taken up was 71 ml. (20°/759 mm.) pressure, which, after allowance for the catalyst, corresponds to 1 approx. mol.

Hydrolysis of 1-benzoyl-1 : 2-dihydroquinoline (0·2 g.) with boiling 15% w/v hydrochloric acid (10 ml.) was complete after 1·5 hr. After cooling, benzoic acid (0·07 g.), m. p. and mixed m. p. 121—122°, crystallised. The filtrate was made alkaline with aqueous sodium hydroxide and extracted with ether. Evaporation of the ether yielded a small quantity of brown oil with an odour resembling that of 1 : 2-dihydroquinoline. No odour of benzaldehyde was detected.

The author thanks Dr. T. Henshall of the Sir John Cass College for his guidance and encouragement, and May & Baker, Ltd., for their laboratory facilities. The semimicro-analyses were carried out by Mr. S. Bance, B.Sc., A.R.I.C., of May & Baker, Ltd.

RESEARCH LABORATORIES, MAY & BAKER, LTD., DAGENHAM, ESSEX.
DEPARTMENT OF CHEMISTRY, SIR JOHN CASS COLLEGE, JEWRY STREET,
ALDGATE, LONDON, E.C.3.

[*Received, May 21st*, 1954.]

Preparation of ωω′-Diphenylpolymethylenes by Anodic Syntheses.

By E. A. Evans and Margaret Whalley.

[Reprint Order No. 5408.]

Few applications of the Kolbe reaction to the preparation of ωω′-diphenylpolymethylenes, Ph·$[CH_2]_n$·Ph, have been reported. Electrolysis of phenylacetic acid in methanol (Linstead, Shephard, and Weedon, *J.*, 1952, 3624) or in methanol and pyridine (Fichter and Stenzl, *Helv. Chim. Acta*, 1939, **22**, 976) gave dibenzyl in 50% yield. The latter workers also obtained 1 : 4-diphenylbutane in 25% yield from β-phenylpropionic acid.

In the present experiments, the conditions employed were essentially Fichter and Stenzl's. β-Phenylpropionic, γ-phenylbutyric, and δ-phenylvaleric acid yielded respectively 1 : 4-diphenylbutane (34%), 1 : 6-diphenylhexane (37%), and 1 : 8-diphenyloctane (47%). The yields thus increase slightly as the series is ascended.

Greaves, Linstead, Shephard, Thomas, and Weedon (*J.*, 1950, 3326) showed that the yield of decanoic acid obtained by electrolysis of mixtures of methyl hydrogen adipate and hexanoic acid increased from 36% when the ratio was 1 : 1 to 58% for a 1 : 6 ratio. In our work electrolysis of a 2 : 1 mixture of β-phenylpropionic acid and γ-phenylbutyric acid gave 1 : 5-diphenylpentane as principal neutral product, and only a small amount of 1 : 6-diphenylhexane; γ-phenylbutyric acid and δ-phenylvaleric acid (2 : 1) gave 1 : 7-diphenylheptane as sole neutral product.

The diphenylpolymethylenes were recovered unchanged after 6 hours' treatment with boiling alkaline potassium permanganate or chromic acid in acetic acid. With nitrating mixture, only 1 : 4-diphenylbutane yielded a crystalline nitro-compound (cf. Fichter and Stenzl, *loc. cit.*).

Experimental.—The electrolysis cell consisted of a cylindrical glass vessel (20 cm. × 3 cm. diam.) containing two parallel platinum electrode plates (2·5 × 2·5 cm.) placed 1—2 mm. apart. The acids were electrolysed at 30—40° for 5—6 hr. in methanol–pyridine (2 : 1) containing a trace of sodium methoxide to act as conductor. Electrolyses using ethanol instead of methanol failed owing to the high resistance of the solution.

1 : 4-*Diphenylbutane.* A solution of β-phenylpropionic acid (20 g.) in technical methanol (50 c.c.) and dry pyridine (25 c.c.) containing sodium methoxide (0·3 g.) was electrolysed until the electrolyte became slightly alkaline [5 hr.; 1 amp.; 120 v (D.C.)], the temperature being kept at 30—40° by cooling the cell in ice-water. The anode slime (1·0 g.) was filtered off and the filtrate concentrated under reduced pressure. Unchanged β-phenylpropionic acid (6 g., 30%), m. p. 47—48°, was recovered. The neutral product was 1 : 4-diphenylbutane (4·8 g., 34%), b. p. 108—109°/0·1 mm., m. p. 51° (Found : C, 91·4; H, 8·7. Calc. for $C_{16}H_{18}$: C, 91·4; H, 8·6%) (Fichter and Stenzl, *loc. cit.*, give m. p. 52°). Nitration yielded the tetranitro-derivative, m. p. 204—205°, described by Fichter and Stenzl (*loc. cit.*).

1 : 6-*Diphenylhexane.* γ-Phenylbutyric acid (20 g.), electrolysed as above, gave unchanged acid (6·3 g., 31%), m. p. 46—48°, and 1 : 6-diphenylhexane (5·3 g., 37%), b. p. 130—132°/0·1—0·2 mm., n_D^{24} 1·5574 (Found : C, 90·5; H, 9·5. Calc. for $C_{18}H_{22}$: C, 90·7; H, 9·3%) (Braun and Deutsch, *Ber.*, 1912, **45**, 1273, give b. p. 206—208°/20 mm.).

1 : 8-*Diphenyloctane.* δ-Phenylvaleric acid (Plati, *J. Amer. Chem. Soc.*, 1943, **65**, 1275) (20 g.) similarly gave unchanged acid (0·9 g., 5%) and 1 : 8-diphenyloctane (7·0 g., 47%), b. p. 138—142°/0·1—0·2 mm., n_D^{23} 1·5290 (Found : C, 89·9; H, 10·0. Calc. for $C_{20}H_{26}$: C, 90·2; H, 9·8%) (Braun and Deutsch, *loc. cit.*, give b. p. 208—210°/8 mm.; Borsche and Wollemann, *Ber.*, 1911, **44**, 3185, and 1912, **45**, 3713, give b. p. 215°/12 mm.).

1 : 5-*Diphenylpentane.* γ-Phenylbutyric acid (14 g.) and β-phenylpropionic acid (7 g.) were electrolysed as before, giving a small amount of 1 : 6-diphenylhexane, b. p. 130—132°/0·1—0·2 mm., and 1 : 5-diphenylpentane, b. p. 114°/0·1—0·2 mm., n_D^{23} 1·5510 (Found : C, 91·3; H, 8·9. Calc. for $C_{17}H_{20}$: C, 91·1; H, 8·9%) (Braun and Deutsch, *loc. cit.*, b. p. 187—189°/10 mm.; Borsche and Wollemann, *loc. cit.*, 190—200°/12 mm.).

1 : 7-*Diphenylheptane.* Electrolysis of a mixture of γ-phenylbutyric acid (8·2 g.) and δ-phenylvaleric acid (17·8 g.) yielded 1 : 7-diphenylheptane (4·5 g., 36%), b. p. 141°/0·6—

0·7 mm., n_D^{23} 1·5445 (Found: C, 90·2; H, 9·4. Calc. for $C_{19}H_{24}$: C, 90·5; H, 9·5%) (Borsche and Wollemann, *loc. cit.*, b. p. 207—208°/12 mm.).

Analyses were carried out in the microanalytical laboratory (Mr. F. H. Oliver) of this Department.

DEPARTMENT OF ORGANIC CHEMISTRY, IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, SOUTH KENSINGTON, LONDON, S.W.7. [*Received, May 25th*, 1954.]

The Synthesis of Sugars from Smaller Fragments. Part VIII. The Synthesis of* D-ido*Heptulosan from* D-*Xylose.*

By J. K. N. JONES.

[Reprint Order No. 5454.]

SOWDEN (*J. Amer. Chem. Soc.*, 1950, **72**, 3325) described how heptuloses may be synthesized from pentoses by condensation with nitroethanol, the resulting heptitol being converted into a heptulose by the Nef reaction (*Annalen*, 1894, **280**, 263). Difficulties in this method are the preparation of the unstable nitroethanol and the isolation of the heptulose. The synthesis has now been simplified and D-*ido*heptulosan isolated in *ca.* 10% yield from D-xylose by the following procedure. D-Xylose was condensed with nitromethane in the presence of sodium methoxide, and the resulting deoxynitrohexitol condensed with formaldehyde. Aldose sugars were then converted by bromine water into aldonic acids, which with the hydrogen bromide were removed on Amberlite resin IR-4B. The resulting mixture of ketoses was fractionated on cellulose (Hough, Jones, and Wadman, *J.*, 1949, 2511), and D-*ido*heptulosan isolated in the usual way (Pratt, Richtmyer, and Hudson, *J. Amer. Chem. Soc.*, 1952, **74**, 2210). D-Sorbose was obtained as a by-product. Other aldehydes may be used in place of formaldehyde and new sugar derivatives produced (unpublished results) (cf. Sowden, *Adv. Carbohydrate Chem.*, 1951, **6**, 318).

Experimental.—Chromatography was carried out on Whatman No. 1 filter paper sheets by the descending method (Partridge, *Biochem. J.*, 1948, **42**, 238), with the solvent systems, (*a*) ethyl acetate–acetic acid–water (9 : 2 : 2), (*b*) butanol–pyridine–water (10 : 3 : 3), and (*c*) butanol–ethanol–water (40 : 11 : 19) (all v/v). Sugars were detected on the chromatogram with *p*-anisidine hydrochloride, ketohexoses with resorcinol in alcoholic hydrogen chloride, and heptuloses with orcinol in a solution of butanol–trichloroacetic acid (Klevstrand and Nordal, *Acta Chem. Scand.*, 1950, **4**, 1320). Evaporation was under reduced pressure. Optical rotations were determined in water at 20° ± 2°.

Condensation of D-*xylose with nitromethane and paraformaldehyde.* D-Xylose (20 g.), methanol (40 c.c.), and nitromethane (72 c.c.) were mixed, a solution of sodium methoxide (6·5 g.) in methanol (140 c.c.) was added, and the whole was shaken for 12 hr. Ether (50 c.c.) was then added and the pale yellow precipitate collected, washed with ether and light petroleum (b. p. 40—60°), and dissolved in water (30 c.c.). Paraformaldehyde (4 g.) was added. When a clear solution had resulted (*ca.* 10 min.) the mixture was poured into sulphuric acid (70 c.c.) [ice (41 g.) plus concentrated sulphuric acid (31 c.c.)]. The solution was then neutralised with barium hydroxide, filtered, and concentrated to *ca.* 250 c.c. Paper chromatography of the solution (solvent *c*) revealed xylose, a hexose moving slightly faster than xylose, heptuloses moving at the rate of xylose and galactose, and a ketohexose moving at about the speed of glucose. Bromine was added to the solution, and oxidation was allowed to proceed for 48 hr. Excess of bromine was then eliminated by aeration and the solution heated at 100° for 1 hr. in order to convert D-*ido*heptulose into the equilibrium mixture of D-*ido*heptulose and D-*ido*-heptulosan. The solution was then cooled and hydrogen bromide and aldonic acids were removed on Amberlite resin IR-4B. The neutral solution was then passed down a column of Amberlite resin IR-120 to remove sodium ions and then down a column of Amberlite resin IR-4B to remove the last traces of acids. The neutral solution was concentrated to a syrup and fractionated on a column of hydrocellulose (24 × 3 cm.) (Hough *et al.*, *loc. cit.*) with butanol, half saturated with water, as mobile phase. Concentration of the appropriate fractions gave

* Part VII, *J.*, 1953, 2140.

fraction I, a syrup (0·1 g.), which gave the reactions of a heptulose sugar and moved at the speed of xylose; it was not further examined. Fraction II (2·75 g.) moved at the speed of arabinose, gave colour tests identical with those of D-*ido*heptulosan, and gradually crystallised. Trituration with methanol gave the crude sugar which was recrystallised from methanol to m. p. and mixed m. p. 174° (2·0 g.), $[\alpha]_D$ −42° (*c*, 2·1). It was chromatographically indistinguishable from D-*ido*heptulosan (solvent *a*, *b*, or *c*). Fraction III (2·7 g.) crystallised; trituration with methanol gave crude D-sorbose. Recrystallisation from methanol gave the pure product (0·9 g.), m. p. and mixed m. p. 164°, indistinguishable chromatographically from an authentic specimen in solvent mixture *a*, *b*, or *c*. Fraction IV (2·2 g.) was a brown syrup, which moved at the rate of galactose (solvent *c*) and gave the colour reactions of a heptulose; it was probably D-*ido*heptulose, which moves at this rate in this solvent.

The author thanks Dr. N. K. Richtmyer for a specimen of D-*ido*heptulosan and the National Research Council, Canada, for a grant.

QUEEN'S UNIVERSITY, KINGSTON, ONTARIO. [*Received, June 10th*, 1954.]

The Kinetics of the Oxidation of Propylene by Nitrogen Dioxide.

By T. L. COTTRELL and T. E. GRAHAM.

[Reprint Order No. 5508.]

THE kinetics of the reaction between nitrogen dioxide and ethylene have been investigated in some detail (Cottrell and Graham, *J.*, 1953, 556). The present note records a similar but less detailed study of the reaction with propylene in the temperature range 160—260° C.

The experimental technique was much the same as before, except for the determination of the nitrogen dioxide concentration as a function of time. The output from the photocell was connected to a rapidly recording potentiometer; the change in photocell output corresponding to the introduction of 12 cm. Hg of nitrogen dioxide caused approximately two thirds full-scale deflection. By this means quite rapid reactions could be followed because the instrument had a response time of about 2 sec., and the chart could be run at about 2 in./min. The recording system was calibrated at the beginning of each run by admitting the nitrogen dioxide stepwise in known amounts until the required pressure was obtained.

The nitrogen dioxide concentration and total pressure were both followed. The nitrogen dioxide concentration falls throughout the reaction, and kinetic analysis was confined to the initial slopes of the curves of nitrogen dioxide against time. The initial rate of disappearance of nitrogen dioxide was nearly proportional to the second power of its concentration and the first power of the propylene concentration, the more accurate exponents being 1·8 and 1·2. An Arrhenius plot of the third-order rate constant (k_3) against temperature gave $k_3 = 10^{9\cdot7} \exp(-13{,}600/\boldsymbol{R}T)$ l.^{2} mole^{-2} sec.$^{-1}$ (160—260°). Below 160° there was an apparent decrease in the activation energy. Surface effects were found to be negligible in the range 190—260°.

At high temperatures there was a pressure rise, while at lower temperatures there was an initial pressure drop followed by a rise, much as in the reaction with ethylene. At the higher temperatures, when there was no apparent initial pressure decrease, the ratio of the pressure increase to the initial pressure of nitrogen dioxide was 0·48. This is to be compared with 0·55 for the reaction :

$$C_3H_6 + 9NO_2 \longrightarrow 3CO_2 + 3H_2O + 9NO$$

The reaction is very similar to that with ethylene, but about 3—4 times faster. This result is in line with the correlation proposed by Walsh (*Fuel*, 1954, **33**, 243) between the ionisation potential of a substrate and the activation energy of its reaction with nitrogen dioxide.

IMPERIAL CHEMICAL INDUSTRIES LIMITED,
NOBEL DIVISION, RESEARCH DEPARTMENT,
STEVENSTON, AYRSHIRE. [*Received, June 30th*, 1954.]

JOURNAL REPRINT SERVICE

THE CHEMICAL SOCIETY · BURLINGTON HOUSE · LONDON, W.1

Original papers published in the *Journal* of the Chemical Society, from January 1954, will be available from the Society in reprint form. Single reprints (without covers) may be obtained at 5*s*. ($0.75) each or books of vouchers can be purchased from the Society at 10*s*. ($1.50) per book or ten books for £4 10*s*. ($13.50). Each book contains five reprint vouchers that are valid for three years and can, during that time, be exchanged for reprints of any five scientific communications published in the *Journal*.

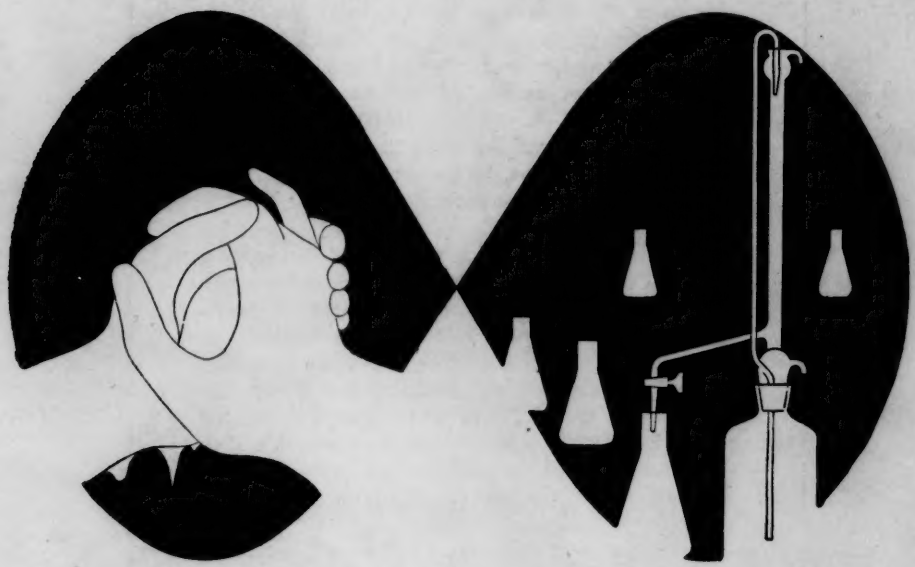
Every paper published in the *Journal* will carry a Reprint Order Number to be used in connection with this service, and the *Proceedings* (issued free each month with the *Journal*) will contain lists of papers accepted for publication. The papers so listed will normally appear in the *Journal* during the next succeeding two months, and if reprints are ordered promptly after the announcement of the title they will be distributed to subscribers at approximately the same time as the issue of the *Journal* in which the papers are published.

It is hoped that this service will enable specialists to obtain quickly reprints of those papers that are of interest to them in their particular branch of chemistry.

Reprints of Lectures published in the *Journal* are not available under the voucher system, but can be obtained price 5*s*. each.

The common test of tincture of soap

"Dr. Clark then exhibited his method of ascertaining quantitatively the comparative hardness of water by means of the common test of tincture of soap, illustrated by experimental evidence, to prove the accuracy of which it is susceptible and the facility of its application."



Dr. Clark gave his demonstration at one of the first meetings of the newly formed Chemical Society in 1841, and the above is an abstract from Volume I of the Proceedings.

The B.D.H. catalogue still includes Clark's Soap Solution and testifies to the remarkable permanence of his technique. Greater accuracy and convenience in total hardness determination, however, are now obtained from the B.D.H. Hardness Solutions and Indicator based on the use of ethylenediaminetetracetic acid as advocated by Schwarzenbach and others.

LABORATORY **B·D·H** CHEMICALS

THE BRITISH DRUG HOUSES LTD. B.D.H. LABORATORY CHEMICALS GROUP POOLE DORSET
LC/P/8

PRINTED IN GREAT BRITAIN BY RICHARD CLAY AND COMPANY, LTD., BUNGAY, SUFFOLK.